QATAR UNIVERSITY

COLLEGE OF PHARMACY

CLINICAL AND PHARMACOECONOMIC ANALYSES OF CDK4/6 INHIBITORS USE IN STAGE IV BREAST CANCER FEMALES IN THE STATE OF QATAR: A COMPARATIVE RETROSPECTIVE OBSERVATIONAL STUDY WITH COST-EFFECTIVENESS AND COST-UTILITY ANALYSES

BY

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ABSTRACT

Al-Ziftawi, Nour, H., Master's: June: [2021], Clinical and Pharmacoeconomic Analyses of CDK4/6 Inhibitors Use in Stage IV Breast Cancer Females in the State of Qatar: A Comparative Retrospective Observational Study with Cost-Effectiveness and Cost-Utility Analyses. Supervisor of Thesis: Mohamed Izham, M., Ibrahim.

Introduction: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are indicated in the first-line treatment of hormonal receptor positive and HER-2 negative (HR+/HER2-negative) advanced breast cancer. Although phase III randomized controlled trials (RCTs) proved their clinical efficacy, they can increase healthcare expenditure. To date, there are no observational studies to validate the clinical findings of the existed RCTs. In addition, only a few pharmacoeconomic evaluations were published regarding the two common CDK4/6 inhibiting agents, palbociclib and ribociclib to evaluate their financial burden.

Objectives: To evaluate the clinical efficacy of palbociclib and ribociclib in the local settings in Qatar. Moreover, to conduct a thorough pharmacoeconomic analysis for the two medications and compare them in terms of their cost-effectiveness and cost-utility.

Methodology: A retrospective observational study on HR+/HER-2 negative stage IV breast cancer patients receiving palbociclib or ribociclib in Qatar was conducted, followed by a comparative pharmacoeconomic analysis. Clinical data were collected from the National Center for Cancer Care and Research (NCCCR) from January 2017 to December 2019 using Cerner ® system. The primary outcomes were progression-free survival (PFS) and overall-survival (OS) generated by Kaplan Meier curves. Safety profiles of both of the two medications were also evaluated. Then, a thorough cost-

analysis was conducted by accounting methodology to summarize the overall cost of the treatment strategies of palbociclib and ribociclib. Costs were obtained from the department of accounting and finance in the NCCCR. To evaluate the long-term costs and effectiveness, a 10-year within-cycle corrected Markov's model was developed. The Markov's model consisted of three main health states: progression-free (PFS), progressed disease (PD), and death. Costs were summarized from the cost-analysis, transition probabilities were calculated from individual patient data obtained in the clinical phase, and utilities were summarized from the published literature. Incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) were compared to a three gross-domestic-product (3 GDP) per capita. Deterministic and probabilistic sensitivity analyses were carried out. Modeling was conducted via TreeAge Pro ® software.

Results: There was no statistically significant difference between the palbociclib and ribociclib groups in terms of PFS; median PFS time was 17.85 versus 13.55 months respectively; $p > 0.05$. Similarly, there was no statistically significant difference in terms of OS between the two medications 29.82 versus 31.72 months; $p > 0.05$. For the pharmacoeconomic analysis, ribociclib dominated palbociclib in yielding an ICER of -83,090.88 QAR per life year gained, and ICUR of -31,868.06 QAR per quality-adjusted life year gained. The results remained robust in all cases of the deterministic sensitivity analyses suggesting ribociclib is more cost-effective than palbociclib. Taking all combined uncertainties into account, the overall confidence in the base-case conclusion was around 60%.

Conclusions: Both treatment strategies have similar efficacy and safety profiles. Nonetheless, ribociclib is a more cost-effective option than palbociclib based on the base-case results and based on the addressed uncertainties related to the model inputs.

DEDICATION

To my mom, the person who believed in me the most and provided all kinds of unconditional love and support!

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1.1.1. Global epidemiology.

Breast cancer is a life-threatening complex disease that is characterized by uncontrolled growth and division of abnormal cells in breast tissues, forming a mass that may be localized or may spread to other tissues (1,2). “In 2018, there were an estimated 17.0 million cases of cancer diagnosed around the world and 9.5 million cancer deaths”, as stated by the American Cancer Society 2020 (3). Breast cancer was the most commonly diagnosed cancer, along with lung cancer, both of which accounted for approximately 2.1 million cancer cases in 2018, separately, which is 11.6% of the total global cancer incidence burden each (4). Breast cancer was also the most commonly diagnosed cancer in women, accounting for 24.2% of cancers in women in 2018 (4). As expected, breast cancer was one of the leading causes of cancer-related death, ranking second with a total estimated number of 627,000 deaths (6.2% of the total cancer-related deaths and 15% in women’s cancer-related deaths) in 2018 (4,5).

Generally, there is a higher incidence and prevalence of breast cancer in developed countries than in developing countries (6). In Europe alone, there were an estimated 404,920 new female breast cancer cases, accounting for 29.2% of the total cancer cases in women in 2018 (6), but the incidence has declined in 2020, accounting for 28.7% of the total cancer cases in women (7). Nonetheless, breast cancer remained the most common cause of cancer-related mortality in women in Europe, accounting for an estimated number of 138,000 deaths in 2018, approximately 92,000 deaths in 2020, and a total estimated number of 475,000 deaths over the period 1990 – 2020 (6–8). In the United States of America (USA), there is an estimated incidence of 276,480 women who will be newly diagnosed with invasive breast cancer and 48,530 new cases

of noninvasive breast cancer in 2020 (1,9). In addition, breast cancer mortality in the USA was the second leading cause of death, accounting for approximately 42,170 deaths in women in 2020 (1,9). There is always a public perception that breast cancer is only a disease of industrialized high-income counties such as European countries and the USA due to the higher incidence there (10). However, most breast cancer-related mortality in the world occurs in low- and middle-income countries (LMICs), accounting for approximately 55% of breast cancer deaths worldwide (10,11).

1.1.2. Epidemiology in underdeveloped countries and Middle East.

Underdeveloped countries, generally low and middle income countries (LMICs), have an increasing incidence rate for breast cancer, and they account for higher breast cancer mortality rates than developed countries (11). Of note, the incidence rates in developing countries such as African, Asian and Central American countries are still lower than those in developed European and American countries (11). For instance, breast cancer was the second leading cause of mortality among women in South Africa in 2016, although it had a lower incidence than developed countries in general (11,12). This may be attributed to poor reporting, lack of early detection, underdiagnosis, or lack of accessibility to treatment options, which are all factors attributed to worsening the prognosis of breast cancer (13).

Middle East countries also fall under the category of developing economies, as listed by the United Nations classification 2020 (14). With no difference from the other developing economy countries, the incidence of breast cancer has risen in the Middle Eastern countries gradually between 1990 and 2016, as well as the mortality rates (15). Breast cancer was ranked as the highest incident cancer in Middle Eastern countries, accounting for approximately 17.7% to 19% of all new diagnoses of cancers in 2018 (16). In addition, it was the leading cause of cancer-related mortality in the Middle East

region, accounting for an estimated total of 48,661 deaths in 2018 (16). From a regional perspective, breast cancer was also at the top of all the diagnosed cancers among females in Gulf Cooperation Council Countries (GCCCs) and the most (17). Alarming trends predict a rising incidence of breast cancer among Arab women since the early 1980s, which can also be predictive of rising future incidence (18). A deeper insight into the local breast cancer epidemiology and clinical overview in Qatar will be discussed later in this chapter, subsection 1.5.

1.2. Breast Cancer Classifications

Breast cancer can be classified into different categories based on different schemes. The classification is primarily based on the histopathological type, the grade of the tumor, the stage of the tumor, and the protein and gene expression status (19). A thorough description of breast cancer would optimally include all of these classification aspects, in addition to other clinical findings, such as signs found on physical examination.

1.2.1. Classification by histopathological type.

The histopathological classification of breast cancer is based on the characteristics of cancerous cells that are seen histologically under light microscopy and where the tumor has arisen from (20). That is, breast tumors can only be limited to the epithelial cells of the breast, which is known as ‘in situ carcinoma’, or they can invade the stroma, which is known as ‘invasive carcinoma’ (20,21). Both in situ carcinoma and invasive carcinoma can be further classified according to where the tumor arises. If a tumor arises from the duct, it is called ductal carcinoma, whereas if it arises from lobules, it is called lobular carcinoma (20,21). As a result, in situ carcinoma can be further subclassified into ductal carcinoma in situ (DCIS) and lobular carcinoma

in situ (LCIS) (20,21). Similarly, invasive carcinoma can be subclassified into invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC) (20,21). In situ carcinoma, with its two subtypes, is the less common type and the more favorable type in terms of prognosis, with five-year survival rates of 97% to 99% (22,23). However, invasive carcinomas are the more common type of breast carcinoma and are associated with lower survival rates than in situ carcinoma, with five-year survival rates of approximately 91%, as estimated in 2020 in the United States (3).

1.2.2. Classification by grade.

The grading of breast carcinomas depends on how much the tumor cells are different from the normal breast tissue cells microscopically (24). Breast cancer cells, similar to all cancerous cells, have their own uncontrolled cell division, leading to different linings and organization compared to normal breast cells (24). Generally, there are three grades of tumors depending on their differentiation and expected prognosis (24,25). If tumor cells are well differentiated, then a tumor is considered low-grade (grade 1) (24,25). If tumor cells are moderately differentiated, then a tumor is considered an intermediate grade (grade 2) (24,25). If tumor cells are poorly differentiated, then a tumor is considered a high grade, which is the least favorable grade and the most associated with poor prognosis (grade 3) (24,25). Lower-grade tumors are associated with a more favorable prognosis and less invasive treatment; therefore, it is important to classify the grade of a breast tumor since it affects the treatment plan in addition to other factors, such as the stage and hormones and gene expression status (26).

1.2.3. Classification by protein and gene expression status.

Cancer cells, including breast cancer cells, experience abnormal growth and proliferation due to having some specific mutations that lead to either overexpression

or reduced expression of genes and/or creation of some receptors of some chemicals. Breast cancer cells can have mutations in some tumor suppressor genes, such as phosphatase and tensin homolog (PTEN), tumor protein p53 (TP53), and breast cancer genes 1 and 2 (BRCA1 and BRCA2); overexpression of an oncogene called human epidermal growth factor receptor 2 (HER-2); and the existence or absence of special estrogen receptors (ERs), progesterone receptors (PRs) or both hormone receptors (HRs) (27–30). Based on this protein and gene expression state, breast cancers were molecularly identified into four major categories: luminal A, luminal B, basal-like, and HER2-enriched (30,31). The luminal A category refers to the type of breast cancer that is HR+ and HER-2 negative, which is the most common type and the most associated with favorable prognosis (30,31). Luminal B is when a breast cancer is positive for both HR and HER-2, which is usually associated with higher grade tumors compared to the luminal A category and poorer prognosis (30,31). The basal-like category, also known as the triple-negative category, refers to this type of breast cancer that is negative for all ER, PR, and HER-2, which is the worst prognosis type and the most common in BRCA1 gene-mutated patients (30–32). The HER2-enriched category refers to breast cancer with HER-2 overexpression with no HR expression (neither ER nor PR) (30,31). This type of classification is very important in determining the treatment plan for patients by either targeted anti-HER-2 therapies, hormonal therapies, or other treatment options and therefore must be combined with other methods of classification (30,31).

1.2.4. Classification by stage.

The aim of cancer staging is to determine the extent and spread of cancer in the body (24). This is particularly important in determining the appropriate treatment option along with patient menopause status and general health and predicting the prognosis and survival of patients (24). The American Joint Committee on Cancer

(AJCC) TNM staging system, which was established since 1959, is the one that is most commonly used in breast cancer staging. As per the last edition of this TNM staging system, it is based on several factors that are all combined together, forming a stage (33,34):

- Primary tumor (T): depends on the size and site of the tumor. There are five categories from T0 (Tis) to T4 that are defined in the AJCC TNM system. Tis is the first category referring to either DCIS ($Tis_{(DCIS)}$) or Paget disease of the nipple ($Tis_{(Paget\ disease)}$). T1 is defined as a tumor of 20 mm or less. T2 is when a tumor is more than 20 mm but less than or equal to 50 mm. T3 category are tumors more than 50 mm. The T4 category is when cancerous cells either invade the chest wall or skin. Additionally, there is the TX category, which means that the primary tumor cannot be assessed (33,34).
- Regional lymph nodes (N): depends on the number, size and location of breast cancer cell deposits in the regional lymph nodes (the axillary lymph nodes, the supraclavicular lymph nodes, and the internal mammary lymph nodes). There are four categories defined by this staging system ranging from N0 to N3. The N0 category means that there are no regional lymph nodes involved. N1 indicates metastasis to a movable axillary lymph node. N2 indicates metastasis in the fixed or matted axillary lymph nodes or in internal mammary nodes in the absence of clinically evident axillary lymph node metastasis. N3 is when there is metastasis in ipsilateral infraclavicular axillary lymph nodes, ipsilateral internal mammary lymph nodes with axillary lymph node metastases, or metastases in supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement (33,34) as follows:
- Metastasis (M): depends on whether there is distant metastasis. There are three

categories of metastasis. M0 is when there is no clinical or radiographic evidence of metastasis. M0 (+i) is when there are cancer deposits in blood, bone marrow, or other nonregional nodes that are no larger than 0.2 mm in the absence of patient signs or symptoms. M1 is when there is any kind of clinical or radiographical metastasis or if there are histologically proven metastases in distant organs or nonregional nodes larger than 0.2 mm (33,34).

- Tumor grade (G): included in the latest AJCC update for the TNM staging system (33,34).
- Hormone receptor status: included in the latest AJCC update for the TNM staging system (33,34).
- Human epidermal growth factor receptor 2 (HER2) status: included in the latest AJCC update for the TNM staging system (33,34).
- Multigene panel: included in the latest AJCC update for the TNM staging system to measure the expression of many genes in breast cancer cells. Oncotype DX has the best available panel and the one included in the latest TNM system (33,34).

After incorporating all these factors, a stage is given to a patient from 0 to 4, where stage 0 represents the localized disease with the estimated best prognosis and 4 represents the metastatic disease with the worst prognosis (33,34). Broader categories of classifications that are based on the disease stage are as follows: early-stage breast cancer (stage I and II A), advanced breast cancer (stage IIB and stage III), and metastatic breast cancer (stage IV). Of note, staging can be pathological, meaning that after examining the tumor characteristics after surgery, or clinical when the surgical option is valid. Although a combination of the two methods is the optimum, clinical staging is the prior method in most cases, especially when determining metastasis

(33,34).

1.3. Breast Cancer Treatment Modalities

The treatment of breast cancer is complicated and may require combinations of different treatment modalities (35). Surgery is considered the mainstay treatment for nonmetastatic breast cancer, unless otherwise contraindicated, in combination with systematic therapy (chemotherapy, hormonal therapy, targeted biological therapy, and immune therapy), radiotherapy, or both. However, the treatment of metastatic breast cancer is usually based on systematic therapy (35). Many factors, including the classification of breast cancer, patient general health status, menopausal status, and diagnosis status, need to be taken into consideration. In this section, the detailed treatment approach for each of the breast cancer types will be explained in more detail.

1.3.1. Breast carcinoma in-situ.

Breast surgery is the standard treatment option for breast carcinoma in situ. There are two types of breast surgery: breast-conserving surgery (BCS) and total mastectomy (35). BCS, also known as lumpectomy or partial mastectomy, is when only the tumor site and some of the surrounding tissues are removed while keeping most of the breast tissues conserved; possibly some of the lymph nodes can also be removed during BCS as a sentinel lymph node biopsy (SLNB) to ensure that there is no further spread of cancer to lymph nodes; however, some guidelines no longer recommend SLNB or any lymph node surgery (35,36). In most cases, BCS is combined with radiation therapy as a part of the standard treatment to decrease the risk of future recurrence, but in some cases where the recurrence risk is low, having no radiation therapy may also be an option (35,37). On the other hand, mastectomy surgery involves the removal of the entire breast (35). It is usually the standard therapy when DCIS or

LCIS is large in size or when there are multiple DCISs or LCISs. SLNB is usually axillary lymph node dissection (ALND), which refers to the removal of many (usually less than 20) underarm lymph nodes. Usually, with mastectomy, radiation therapy is not needed (35). Nonetheless, all women should be educated about breast reconstruction surgery, i.e., a surgery for rebuilding the shape and look of a breast, as a part of their treatment; however, it is not a decision that should interfere with the main mastectomy surgery decision (35,36). For systematic therapy, hormonal therapy with tamoxifen or an aromatase inhibitor such as letrozole at older ages (>60) can be considered to lower the probability of recurrence if a patient has luminal breast cancer (positive for ER or PR or both) (38,39).

1.3.2. Invasive breast carcinoma.

1.3.2.1. Stage I, II (early-stage breast cancer).

1.3.2.1.1. Surgery.

Similar to in situ breast carcinoma, surgery is considered the primary treatment for early-stage breast cancer (35,36). BCS with SLND or a total mastectomy with or without ALND can be the two surgeries that are indicated for this type of patient (35,36). The selection between these two options depends on the general clinical status of a patient, tumor status, the preference of the patient, and a patient's eligibility/ineligibility for a certain type of surgery over another (35,36). A patient is not eligible for BCS and rather is indicated for mastectomy if the tumor is multicentric, a tumor is of a large size compared to breast size, a patient has a diffuse malignant-appearing calcification on imaging, a patient has a prior history of chest radiation therapy, or a patient is a pregnant (35). In these cases, a patient undergoes a mastectomy as the primary indicated type of surgery (35). Additionally, a patient undergoing mastectomy surgery is to be educated about the option of having breast reconstruction

surgery as a part of the treatment plan if they opt to, but their decision should not affect the clinical decision of mastectomy (36,40).

1.3.2.1.2. Radiation therapy.

The aim of adjuvant radiation therapy is to prevent future breast cancer recurrence by eradicating local subclinical residuals that may have not been eradicated by surgery (35,36). Typically, adjuvant radiation therapy is indicated as a first-line treatment along with BCS (35,36,41). There are two types of radiation therapy with BCS: conventional radiation therapy, which itself can be whole-breast external beam radiotherapy (EBRT) or partial breast irradiation (PBI), and brachytherapy (35,36,40). In conventional radiotherapy, a patient is supplied with adjuvant radiotherapy from an external source for a duration of three to six weeks post-surgery depending on the dose and the type (EBRT or PBI) (35,36,41). Brachytherapy, also known as internal irradiation, can be an alternative to conventional radiotherapy (35,36). It is a single dose of radiotherapy delivered during or just after surgery that precisely targets the tissues where there is the highest risk of cancer recurrence, but it is limited to patients with a low risk of recurrence (35,36,42). On the other hand, postmastectomy radiation therapy is not often a part of the standard treatment and is only indicated if a patient is classified as a high-risk patient for carcinoma recurrence (35,36,41,43). High-risk patients mainly include patients with postmastectomy positive margins, patients with a primary tumor of more than five centimeters, and patients with involvement of four or more lymph nodes (35,36,40).

1.3.2.1.3. Systematic therapy.

Systematic therapy can be administered in neoadjuvant settings, i.e., before the surgery, or adjuvant settings for early breast cancer patients (36,40). Normally, neoadjuvant drug therapy, often chemotherapy, is used in early-stage breast cancer only

when a tumor is large and a patient is to receive BCS; this is to make BCS more feasible (36,40,44). All patients with early-stage breast cancer receive adjuvant systematic drug therapy. Adjuvant drug therapy is to be started 3–6 weeks postsurgery and should not be delayed since delay (>12 weeks) was shown to be associated with less favorable outcomes in terms of overall survival and relapse-free survival (40,45). The choice of adjuvant therapy depends on a patient's menopausal status and tumor type as follows:

- Luminal A type (HR positive and HER-2 negative): in this type of cancer, adjuvant hormonal therapy alone is usually sufficient unless there is a high disease burden (1–3 involved nodes coexisting with many other high-risk factors, 4 or more positive nodes, or a high recurrence score on estimators such as Oncotype DX) (36,40). In the case of this high burden disease, adjuvant chemotherapy followed by adjuvant hormonal therapy is the option of treatment (36). The selection of hormonal therapy also depends on menopausal status and general patient status (36,40). The 5–10-year tamoxifen is the optimum treatment for premenopausal women; nonetheless, if a patient became postmenopausal during the first 5 years of tamoxifen, there should be a switch to aromatase inhibitors (AIs) such as letrozole (40). For a postmenopausal patient, AIs and tamoxifen are considered standard treatments. There are several ways to use AIs and tamoxifen in postmenopausal women: upfront (nonsteroidal AI such as anastrozole and letrozole, or exemestane), after 2–3 years of tamoxifen, or as extended adjuvant therapy, after 5 years of tamoxifen (only letrozole and anastrozole) (40). The standard hormonal therapy duration in postmenopausal women is five years (40). However, there is a high recommendation to use extended hormonal therapy for up to 10 years since it is associated with a lower risk

of disease recurrence and contralateral breast cancer; nonetheless, there is a risk of treatment-related side effects such as osteoporosis and thrombotic events (40,46). Therefore, the risk-benefit relationship should be evaluated and discussed with patients before making a decision regarding extended hormonal therapy (40).

- Luminal B (HR positive and HER-2 positive): in the majority of patients with the luminal B subtype, a combination of chemotherapy, endocrine therapy, and anti-HER2 therapy is considered the standard therapy (36,40). Nonetheless, in specific low-risk patients (T1abN0), the combination of anti-HER2 therapy and endocrine therapy alone may be used as the standard treatment (36). As highlighted in luminal A above, the selection of hormonal therapy agents and duration depend on a patient's menopausal status. For anti-HER-2 therapy, also known as targeted therapy, trastuzumab alone is used in most cases. However, trastuzumab can be combined with pertuzumab for high recurrence risk patients.
- HER 2-enriched (HR negative and HER-2 positive): in this type of patient, anti-HER-2 targeted treatment of one year of trastuzumab with or without pertuzumab (depending on a patient's recurrence risk) plus chemotherapy is to be given to patients. Trastuzumab is typically administered for 1 year; however, some studies have compared it to 6-month regimens and found no inferiority in terms of disease-free survival (40,47). Usually, chemotherapy is administered for 12–24 weeks (4–8 cycles) depending on the chemotherapy regimen and the patient risk of recurrence. For most patients, a sequential anthracycline/taxane-based regimen is the standard therapy (40).
- Basal type (triple negative): for this type of patient, only adjuvant

chemotherapy is indicated as the sole option for treatment (36,40). A sequential anthracycline/taxane-based regimen is the standard therapy for 4–8 cycles (40). However, in some specific patients with a low risk of recurrence or experiencing toxicities such as cardiac complications, nonanthracycline regimens can be considered the standard (40).

1.3.2.2. Stage III (locally advanced breast cancer).

1.3.2.2.1. Neoadjuvant therapy.

The aim of neoadjuvant therapy in stage III is to decrease the size of the primary tumor in the breast to make the tumor operable by surgery (36). Therefore, systematic drug therapy is given to patients prior to possible surgery to decrease the tumor load (36). However, not all patients with locally advanced disease are eligible for neoadjuvant therapy (36). Patients are eligible for adjuvant therapy only if the tumor is operable and a patient is willing to have BCS but the tumor size is large, or if the tumor is inoperable but the patient has a T4 tumor, N2 or N3 regional node involvement, or inflammatory breast cancer (36). Based on patient eligibility for neoadjuvant tumors and based on tumor characteristics, a new adjuvant regimen was developed (36). For a very strongly positive HR and HER-2 negative status, a single endocrine therapy can be given as a neoadjuvant in postmenopausal women or for premenopausal women with ovarian suppression for up to 24 weeks (36); however, the benefit of a single endocrine neoadjuvant for premenopausal women may be dubious, so neoadjuvant chemotherapy should be considered (36,48,49). For HER-2-positive tumors, most often, a combination of anti-HER-2 (trastuzumab with or without pertuzumab) with sequential chemotherapy is the standard neoadjuvant since it has shown better outcomes than chemotherapy alone (36,50). For HER-2-negative tumors, chemotherapies that are typically used as adjuvants can also be used as neoadjuvants (36).

1.3.2.2.2. Surgery.

For all patients receiving neoadjuvant therapy, the response should be evaluated periodically, and the surgery decision should be made accordingly (36). If there is disease progression during preoperative neoadjuvant therapy, a patient should be shifted to surgery immediately without waiting for the full duration of neoadjuvant therapy (36). If no disease progression occurs, a patient undergoes surgery after neoadjuvant therapy (36). Surgery can be a BCS or a total mastectomy depending on the tumor size and the response to neoadjuvant treatment (36).

1.3.2.2.3. Adjuvant therapy.

After surgery, adjuvant treatment with systematic drug therapy, radiation therapy or both should be considered as a part of the standard care. The selection of adjuvant treatment is based on a patient's response during neoadjuvant treatment as well as tumor characteristics (36). Patients can experience either disease progression during neoadjuvant therapy, partial response, which means a decrease of 30% or more in the largest tumor diameter, or a complete response, which means full eradication of the tumor target in the breast. If a patient experiences a complete response or a partial response to the degree of making lumpectomy feasible, then adjuvant treatment involves both radiation therapy for the whole breast with or without the supraclavicular and infraclavicular area (depending on the lymph nodes involved) and systematic drug therapy based on the tumor type (36). However, if a patient achieves a partial response but not up to the degree of allowing lumpectomy and the patient undergoes mastectomy surgery, adjuvant treatment involves both radiation therapy for the chest walls, the supraclavicular and infraclavicular area, the internal mammary nodes, and the axillary bed at risk (depending on the lymph nodes involved), followed by systematic drug therapy based on the tumor type (36). Systematic drug therapy depends on the tumor

status. For HR+ HER-2-negative tumors, endocrine therapy with 5-year tamoxifen or 5-year tamoxifen plus ovarian suppression is considered the standard care for premenopausal women, and the duration can be extended based on the risk-benefit (36). For postmenopausal women with HR+ and HER-2-negative breast cancer, AI (anstrazole or letrozole) for 7.5 to 10 years, sequential tamoxifen for 4.5–6 years followed by AI to complete a total duration of therapy for 10 years, 2–3 years with tamoxifen followed by AI to complete the 5 years, or 2–3 years with AI followed by tamoxifen for 5 years are all options of standard care, noting that the extended duration of therapy is more recommended due to more favorable clinical outcomes (36,51). For HR-negative HER-2-positive tumors, one year of targeted therapy with trastuzumab, with or without pertuzumab, is considered the standard care (36). For both HR- and HER-2-positive tumors, one year of targeted anti-HER-2 therapy with standard endocrine therapy based on the menopausal state is the standard care (36). For triple-negative breast cancer, either careful follow-up in the case of a neoadjuvant complete response, adjuvant chemotherapy with capecitabine, or for capecitabine toxicity, several regimens, such as taxane and anthracycline-based regimens, or classical CMF (cyclophosphamide, methotrexate and 5-fluorouracil), may be considered in the case of a noncomplete response and are considered the standard care (36,52).

1.3.2.3. Stage IV (metastatic breast cancer).

1.3.2.3.1. Surgery.

Surgery is not the primary treatment option for standard care in stage IV breast cancer, although some studies have suggested a clinical benefit for the removal of the primary tumor in metastatic settings (36,53). However, it can remain an option as a palliative therapy in cases of any pain or discomfort associated with the breast tumor area (36). The major type of surgery in this case is mastectomy. Nonetheless, the need

for mastectomy in this case may be replaced by radiation therapy (36).

1.3.2.3.2. Radiation.

Similar to surgical treatment, local radiation therapy for primary breast tumors is not often the standard care provided to metastatic breast cancer patients, although there is a suggested clinical benefit associated with radiation of the primary tumor (36,54). However, radiation therapy is still used in metastatic breast cancer as a palliative therapy for some other parts where cancer has spread, especially if a tumor in a specific area does not respond to systematic therapy (36). Some of the areas that can be targeted by radiation are the spinal cord in cases of spinal cord compression, bones of arms or legs in cases of cancer spreading to bones, and the brain in cases of metastasis (36).

1.3.2.3.3. Systematic therapy.

Systematic drug therapy is considered the mainstay treatment for stage IV breast cancer. The selection of drug therapy depends mainly on the tumor type, diagnosis type whether it is for the first time (de novo), or it is recurrent, and the patient general clinical status. For patients with HR+/HER-2-negative breast cancer, all postmenopausal patients and premenopausal patients are to receive hormonal therapy with or without targeted cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6 inhibitors) as a first-line option, with a recommendation for premenopausal women to receive ovarian suppression or ablation as well. However, if there is a visceral crisis, i.e., cancer metastasis to organs to the degree of not allowing them to function, chemotherapy with anthracycline, taxane-based regimens, or antimetabolites with or without new biological agents or targeted therapies are recommended. For HER-2-positive patients, anti-HER-2 with trastuzumab or its biosimilars, with or without pertuzumab (depending on a patient's tumor load), has also been shown to provide greater survival benefit than

chemotherapy. Nonetheless, chemotherapy is also preserved in cases of disease progression or visceral crisis. For both HR+ and HER-2-positive patients, the standard treatment is often a combination of endocrine and anti-HER-2 medications, endocrine therapy only if the tumor is very strongly positive for HR compared to HER-2, or a combination of anti-HER-2 and chemotherapy. Last, for triple-negative breast cancer, chemotherapy is the only option for treatment. Often, multiple lines of chemotherapy are given to patients until disease progression or severe toxicity. In all types and under all the different lines of treatment, if a patient had a bone disease, then calcium, vitamin D, and either denosumab or zoledronic acid or pamidronate should be administered along with systematic cancer treatment. Below is a more elaboration about the agents/regimens used in the treatment of stage IV breast cancer:

- Endocrine therapy

  The main endocrine therapies used in stage IV breast cancer are antiestrogens [selective estrogen receptor modulators (SERMs) such as tamoxifen and selective estrogen receptor degraders (SERDs) such as fluvistrant] and AIs such as anstrazole and letrozole. As a first-line therapy for stage IV breast cancer, these agents (except for tamoxifen) are indicated to be combined with CDK4/6 inhibitors or to be given alone. Nonetheless, for premenopausal and perimenopausal women, ovarian ablation or ovarian suppression with luteinizing hormone-releasing hormone (LHRH) agonists is often needed with first-line endocrine therapy. Often, the duration of endocrine therapy is until a patient develops disease progression or intolerable side effects. If a patient developed disease progression on three different lines of hormonal therapies with their combination, a patient's tumor would be called 'hormone resistant'. In case of hormone resistance, a patient is shifted to chemotherapy or only a

follow-up with supportive care.

- HER-2 targeted therapies

  There are two main types of anti-HER-2 drug therapies: HER-2 antibodies (trastuzumab and pertuzumab) and HER-2 inhibitors (lapatinib and neratinib). HER-2-targeted therapies can be used alone, in combination with endocrine drug therapies, or with chemotherapies, depending on the tumor type and disease progression (36).

- Chemotherapy

  There are different regimens of chemotherapy to be used in the treatment of metastatic breast cancer depending on a patient's tolerability and disease progression for one regimen over another. The options include anthracycline-based regimens (doxorubicin and epirubicin), antimetabolite-based regimens such as CMF, alkylating agent-based regimens such as carboplatin and cisplatin, and several other chemotherapeutic-based regimens (36). Often, the duration depends on the regimen selection, patient tolerability and disease progression (36).

- Immune therapy

  This class of systematic therapies is also considered a targeted therapy that targets tumor cell immunity by inhibiting an enzyme that is expressed in tumor cells and mediates immune cell formation, the PD-L1 enzyme (55). Atezolizumab is one of the agents under this class that was approved for use in advanced triple-negative breast cancer patients with positive PD-L1 enzyme in combination with nab-paclitaxel due to the proven prolonged progression-free survival (36,56). However, it is still associated with multiple immune-mediated serious side effects; therefore, close monitoring is always required (36).

- Other targeted therapy

1. CDK4/6 inhibitors: CDK4/6 inhibitors are a relatively new class of medications that target cyclin-dependent kinase 4 and 6 enzymes, which are important enzymes in the tumor cell cycle, so inhibiting them leads to cell viability. Three agents have been approved as first-line treatments for stage IV breast cancer (36). Palbociclib was the first CDK4/6 inhibiting agent approved in 2015 as a first-line treatment for stage IV breast cancer in combination with AI or fulvestrant in postmenopausal women (57). Later, in 2017, ribociclib was introduced to the market for the treatment of stage IV postmenopausal women with the same combinations of palbociclib, but in mid-2018, the use was expanded to pre/perimenopausal women (58). Ambeciclib is the only CDK4/6-inhibiting drug that can be administered alone or along with endocrine therapy for the treatment of stage IV breast cancer (59). All three CDK4/6 inhibiting agents showed more favorable outcomes when combined with AI or fulvestrant in terms of prolonged survival compared to their comparator endocrine therapy alone (60–67). Although these agents are associated with clinical benefit, they can be associated with multiple serious blood side effects, cardiac arrhythmias, and many other side effects that can lead to toxicities, so regular monitoring is always required (36).

2. mTOR inhibitors: Everolimus is an mTOR-inhibiting drug. The inhibition of mTOR enzyme leads to improved resistance of cancer cells to hormonal therapy and downregulation of cancer cell growth (68). Therefore, everolimus is an mTOR that was approved in the use of HR+/HER-2-negative women with breast cancer and often more approved for those who previously developed resistance to hormonal therapy (68).

3. PARP inhibitors: Poly ADP-ribose polymerases (PARPs) are a group of enzymes that are able to repair cancer cells and hence prevent their mortality. BRCA1/2 activates the release of these PARPs (69). Therefore, PARP inhibitors (olaparib and talazoparib) are indicated for the treatment of patients with metastatic breast cancer and BRCA1/2 mutations and HER-2-negative patients (36). It was shown that both agents showed superiority over chemotherapy in terms of progression-free survival (69,70).

1.4. Pharmacoeconomics

1.4.1. Pharmacoeconomics and decision making.

Decision analysis is a systematic approach that is concerned with the identification, assessment, and representation of key features of a decision and can be quite helpful when facing decisions (71). Therefore, decision analysis is considered an important tool to inform the decision-making process under conditions of uncertainties in terms of outcomes or risk/benefit balance (71). In the health field, the process of decision making should be well informed since health systems are complex due to being dynamic in nature, meaning that they are prone to be influenced by many factors, including changing populations, changing economic status, changing patterns of diseases, and the increased availability of new treatments and technologies with their possible various outcomes (72). Health economics is considered a tool for decision analysis and is defined as a sector of health that identifies, compares, and measures different options in health in terms of their costs and consequences (73). It is important for the decision-making process since it meets the dynamicity of healthcare systems and guides the most efficient use of available resources to obtain the best outcomes, taking uncertainties associated with health systems into consideration (73,74).

Pharmacoeconomics is a subdiscipline of health economics that is concerned with the comparison and analysis of costs to the related consequences of drug therapy options and strategies (75). Pharmacoeconomics is specifically important due to the increasing drug therapeutic options and their costs, which are estimated to account for at least 10% of the total health expenditures of each country (76). In the United States of America (USA), drug therapy was the third highest in national health expenditure in 2017 after hospitalization cost and physician and clinical services cost, accounting for $333.4 billion out of the total health expenditure of $3.5 trillion (77). Therefore, several decision-making institutions, such as the National Institute of Health and Clinical Excellence (NICE), have endorsed pharmacoeconomics, specifically cost-effectiveness evaluations, as an important part of their decision-making process (78). By convention, all pharmacoeconomic evaluations are comparative in nature, meaning that a single treatment option cannot be analyzed on its own; there should be at least two options for which an 'incremental analysis' can be conducted between the various options with consideration of the benefits as well (73). More elaboration regarding the types of costs and evaluations in pharmacoeconomics will be further discussed.

1.4.2. Costs and benefits in pharmacoeconomics and health economics.

As mentioned earlier, a comprehensive pharmacoeconomic analysis should involve both cost and benefit analyses. There are several types of costs that are incorporated in pharmacoeconomic analyses that are related to healthcare resources or nonhealthcare resources and can be classified as follows (79):

- Direct medical costs refer to the exchange monitorial value of the consumed medical resources or services. This includes but is not limited to medication costs, clinical service costs, medical procedure costs, laboratory test costs, hospitalization costs, and intervention and intervention monitoring costs.

- Direct nonmedical costs include all the costs that are not associated with medical services but need to be paid to receive medical care. For example, travel costs to receive healthcare, transportation costs, hotel stays, and childcare, etc.
- Indirect costs include the cost of lost productivity, lost earnings, lost leisure by a patient (or patient caregiver), or society to receive medical care.
- Intangible costs reflect unphysical costs such as the cost of treating pain, worrying, or distress to patients or their families.

Regarding the benefits, in one pharmacoeconomic analysis, all outcomes should be measured in the same units to ensure a fair comparison. The most common units of measuring outcomes are as follows:

- Natural units are indicative of years of life saved, disease conditions prevented, and death prevented.
- Utility units are usually based on a part or a whole measurement of patient quality of life. Often, it is combined with natural units to have quality-adjusted natural units, e.g., quality-adjusted life-years (QALYs).
- Associated economic benefit transforms all the benefits into monetary units that are used in specific types of pharmacoeconomic analysis.

The selection of a certain type of cost over another, or one type of outcome over another, depends on the perspective from which a pharmacoeconomic analysis is conducted, meaning that the value of the pharmacoeconomics analysis relates to the recipient to whom it would matter; i.e., would it matter for a patient, healthcare provider, or for the whole society (80). Most often, healthcare provider perspectives are being used since they are the easiest and the most important to decision makers; however, the societal perspective is the most inclusive context and would provide more comprehensive outcomes for patients, their families, the public, and

government/health-system expenditures and benefits (80). All types of pharmacoeconomic analyses can use any type of the listed costs above (numerator), but they would differ according to what unit they use to measure the benefit (denominator) and accordingly would differ in the type and the incremental analysis unit, as shown in 1.5.3.

1.4.3. Paradigms of pharmacoeconomics and health economics evaluations.

Since pharmacoeconomics studies basically analyze resources (incomes/outcomes), there were many classifications for the paradigms used in pharmacoeconomics. The four main categories are as follows (73,81,82):

- Cost-effective analysis (CEA): This category studies both the outcomes versus the cost of two different interventions. Costs are often measured in monetary units, and benefit is measured in natural units. It is often measured by the incremental cost-effectiveness ratio (ICER). Although cost effectiveness is the most common type of pharmacoeconomic evaluation, it has a major limitation in that it cannot be used in the comparison of two different interventions with different outcome measures.
- Cost-utility analysis (CUA): It is also concerned with the study of outcomes versus costs, but benefits are measured by utility units, so it takes a patient's quality of life into consideration with the common utility unit (QALY). It is often measured by the incremental cost-utility ratio (ICUR), which is used to express the incremental cost to the additional QALY gained by a patient owing to the use of the intervention of interest. Although this type of analysis takes patient quality of life into consideration, there is a range of subjectivity associated with it due to the different estimators for the quality of life among patients.

- Cost benefit analysis (CBA): This category also analyzes the outcomes versus costs, but it focuses on the financial value of the benefits, so both costs and benefits are measured in monetary units. It is often measured as a cost-to-benefit ratio (C:B) or net benefit ratio. This method allows the comparison of different outcomes with different measurement units, as it ultimately unifies all the units into monetary units. However, it is associated with difficulties in practice.
- Cost minimization analysis (CMA): in this category, two identical alternatives in terms of outcomes are thoroughly compared to decide the least cost alternative. The disadvantage of this method is that it assumes that both alternatives have the exact same outcomes, which may not be feasible in real practice.

All these types of pharmacoeconomic analyses may utilize published clinical trials, medical records, decision analytic models or a combination of all these to conduct the intended pharmacoeconomic evaluation (73). The yield of these analyses is often a monetary value that is compared to what is called 'threshold'; meaning the monetary value that can be paid for achieving a certain outcome by using an alternative over the other (73). Modelling is now of the most common tools used in pharmacoeconomics to perform these types of analyses, and therefore, further elaboration about modeling and special considerations will be further explained.

1.4.4. Modeling tools and important consideration.

According to The International Society for Pharmacoeconomics and Outcomes Research (ISPOR), decision analytical modeling can be defined as "an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources, and whose purpose is to estimate the effects of an intervention on valued health consequences and costs" (83). In the

health field, decision modeling is useful in circumstances where there are no available clinical trials or in circumstances where trials are not available but without the inclusion of economic data to synthesize the best available information related to both cost and outcomes (84). Decision tree and Markov models are two of the most common decision analysis modeling tools used in pharmacoeconomic evaluations (73,84). Therefore, this section discusses these two tools in more detail.

- Decision tree (84,85)

  In the decision tree analytical model, all the different alternatives in a specific treatment strategy, with their possible outcomes, and the probability of occurrence of each outcome, are identified, and then the economic and outcome value of each treatment option is calculated. This is to anticipate the real-life scenario of using alternative treatment options. Based on the total calculated outcome of a total treatment arm and the calculated economic value, an incremental cost/outcome analysis takes place to make a decision to favor one treatment alternative over the other. A visual representation of a simple decision tree model is presented in Figure 1. As shown in the figure, the square represents a ‘decision node’ where the different alternatives are represented, the circles represent ‘chance nodes’ where the different outcomes of the different alternatives are generated by chance or a probability that is called ‘transition probability’, and the triangles represent ‘terminal nodes’, where the health impact of each consequence, called a payoff, is quantified. Although decision trees are a systematic comprehensive model, they have a major limitation in that they are not suitable for long-term outcomes or long-duration events (73).

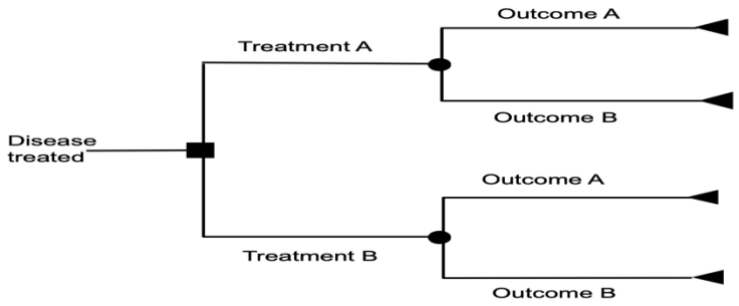

Figure 1. Visual simple representation of decision-tree analysis

- Markov Model (73,84)

  The Markov model is considered the most commonly used decision analytical model in health economics. It is often composed of several ‘states’ to represent all the possible outcomes of a specific intervention. These states are assumed to be mutually exclusive such that a patient can be only in one state in a given time of the model. For example, if a model is composed of health states of disease-free survival, disease, and death, a patient can be in one and only of these three disease states in a given time of a model. However, a patient can move from state to another, which is controlled by a calculated or an estimated probability; it is called ‘transition probability’. Patient movement from one state to another is assessed at specific time periods of the models, which are called ‘cycles’, and the length of a cycle is determined by a pharmacoeconomics specialist. At the end of each cycle, a patient can remain in the same health state, move to another subsequent state, or move to a terminal state directly depending on the assumption of a model. Values assigned to each state depend on the time spent on this state and represent both cost and utility; these values are called ‘Markov rewards’. Therefore, costs and benefits can be summarized and incremented at the end of the model to serve a specific purpose of a specific type of analysis. A

simple representation of a Markov model is illustrated in Figure 2. The Markov model is not limited to a specific time; it analyzes patients until they all reach the terminal state or is based on the time horizon that the analyst sets for the model. Therefore, its major advantage is that it is suitable for extended-time outcomes.

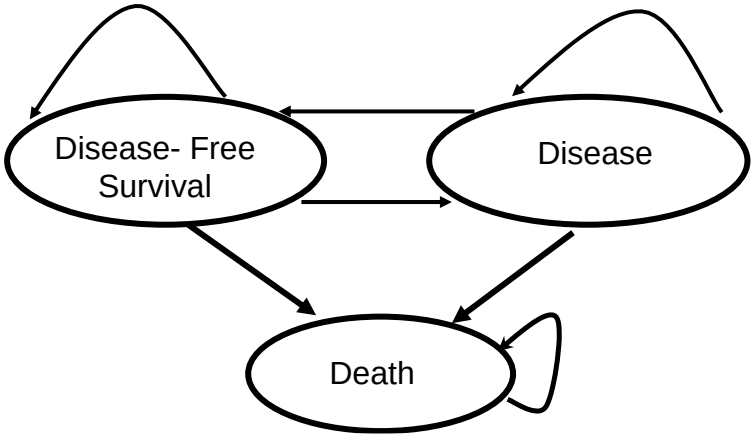

Figure 2. Visual simple representation of a Markov's model

Although modeling represents one of the most pharmacoeconomic decision analytical tools, it is worth remembering that modeling tries to reach the real case scenario with anticipated outcomes, but it is not truly a real scenario. Therefore, there are some special considerations to be taken into consideration as follows:

- Discounting (85)

  In all modeling-based pharmacoeconomic analyses, all the cost and outcome measurements associated with the alternative options that are compared are collected at a specific time (baseline). However, the values of these costs and outcomes differ over time, meaning that they become less valuable in the future. Therefore, adjusting these values in relation to time is undertaken, which is

called ‘discounting’. Generally, the discounting rate differs annually based on the setting, but it is appreciated to be between 3% and 5%.

- Uncertainty (85,86)

  As mentioned earlier, because modeling studies are based on informed conjectures, they are associated with a degree of uncertainty. Therefore, sensitivity analyses are often conducted to ensure the robustness of a certain conclusion against uncertain model inputs. There are some common types of sensitivity analyses. The univariate sensitivity analysis is concerned with the uncertainty of only one input variable, whereas the multivariate sensitivity analysis is concerned with more than one variable uncertainty. There is also another type of sensitivity analysis called the threshold sensitivity analysis value, which is concerned with the analysis of the value of one or more inputs, above or below which the conclusion of the analysis would differ in favor of a specific intervention. A last common type of sensitivity analysis is probabilistic sensitivity analysis, in which each input parameter is assigned a specified distribution, which is randomly collected together, yielding different scenarios; this analysis is most commonly performed by Monte Carlo methods.

1.4.5. Economic burden of breast cancer treatment.

The economic aspect of breast cancer medications is very important due to their very high cost, similar to all cancer medications. According to the National Institute of Health (NIH), most of the cancer medications from 1995–2014 were priced at an average of $100,000 per patient for one year of treatment and are still increasing (87). For breast cancer, the economic burden is substantial, and in most countries, it depends on the stage and country settings. In countries such as Canada, the USA, Portugal, and the United Kingdom, the treatment of breast cancer with stage IV metastasis has costed

approximately twice as much as the early stages over the past two decades; however, the discrete amount of money was variable across the different settings (88). In the USA in 2010, only the direct medical costs associated with metastatic breast cancer were estimated to be approximately $4.2 billion per year (89). Although spending on cancers, including metastatic breast cancer, is generally lower in less developing countries such as the Middle East, it still represents a main health concern (90) and therefore needs to be based on more established economic studies.

1.5. Status and Clinical Practice in Qatar

1.5.1. Qatar country economic profile and healthcare system.

Qatar is an independent Arab country located in the Middle East region, Gulf area, continent of Asia. In 2020, according to the United Nations classification, Qatar is considered as a country with a developing economy (14). However, it is one of the richest countries with an estimated increasing growth domestic product of 3.1% and 4% in 2020 and 2021, respectively (14). As per the recent data provided by the World Bank in 2017, Qatar spent 2.61% of its total GDP as health expenditure (91). This is increasing spending compared with 2014 (91); for instance, it can be anticipated that healthcare expenditure will still increase as long as investment continues to increase in Qatar over the upcoming years.

The healthcare system in Qatar is a nonprofit healthcare system in which it is the main payer for healthcare services to all citizens and residents (92). Hamad Medical Corporation (HMC) is the main healthcare provider in Qatar that offers its services through three main levels: i) primary healthcare centers, ii) specialized clinics, and iii) hospitals (governmental) with their associated pharmacies (92). Cancer care is mainly provided by the National Center for Cancer Care and Research (NCCCR), which is the premier hospital for managing cancer in the state of Qatar and one of the main hospitals

under HMC (93).

1.5.2. Epidemiology of breast cancer in Qatar.

In Qatar, breast cancer was at the top of all cancers in 2018 in both genders, accounting for 31% of the total new cases of cancers (94). The incidence of breast cancer itself witnessed a dramatic increase of 52% from the 1990s to 2006 (95). This can be attributed to many factors, such as economic progression, urbanization, and lifestyle changes (96). Unfortunately, to our knowledge, there are no available local epidemiological or financial studies about the subtypes of breast cancer. Nonetheless, expectedly, similar to other countries, breast cancer would pose the highest financial expenditure compared to early-stage breast cancer. The management of breast cancer in Qatar is similar to the international guidelines. For metastatic breast cancer, systematic drug therapy is the main treatment, but it depends on the subtypes of breast cancer in terms of HER-2 gene expression and HR status (highlighted in 1.3.2.3); however, for the CDK4.6 inhibitors that are used in first-line therapy, only palbociclib and ribociclib are available in Qatar. Palbociclib has been a formulary medication since late 2017; however, ribociclib was recently added to the formulary in early 2020. To our knowledge, the addition of these medications into the formulary was only based on the published effectiveness from clinical trials, without any analysis of their economic aspects. Therefore, the clinical and economic aspects of the treatment of metastatic breast cancer in Qatar, specifically first-line breast cancer, including CDK4/6 inhibitors, should be addressed by future research.

1.6. Study Rationale

Due to the nature of the healthcare system in Qatar where the governmental section is the major healthcare provider, the government pays for most of the medical fees on behalf of the patients for all diseases and fully bears the expense of cancer

medical care on behalf of the patients. Additionally, as mentioned earlier in '1.3.2.3.3', CDK4/6 inhibitors are a relatively newer class of medications that are used in the first-line treatment of HR+, HER-2-negative metastatic breast cancer patients. Palbociclib and ribociclib are the only authorized CDK4/6 inhibitors used in the treatment of this breast cancer population in the State of Qatar. Both medications need frequent close monitoring due to their side effects, which include blood-related side effects (such as neutropenia, febrile neutropenia, thrombocytopenia, anemia, and leukopenia), heart-related side effects (such as affecting the QT interval and induced abnormalities in electrocardiography), gastric side effects (such as diarrhea and constipation), and generalized fatigue and neurological pain (57,97). Therefore, although these agents provide clinical benefit, they can increase drug expenditure and health care costs (98). Thus, it is important to investigate whether palbociclib and ribociclib are cost effective for their use and compare their cost-effectiveness differences in Qatar. To our knowledge, there are no pharmacoeconomic analyses regarding these two drug agents or regimens containing them in the state of Qatar, nor in the Gulf or Middle Eastern countries. A deep literature review will be illustrated in Chapter 2 of this thesis.

1.7. Study Objectives

The overall goal of this research is to provide the decision makers with a robust evidence from the clinical and the pharmacoeconomic point of views to decide regarding the use of palbociclib and ribociclib in the clinical settings in Qatar. The evidence will be by carrying out a thorough clinical and pharmacoeconomic evaluations of the only two CDK4/6 inhibitors in use in Qatar, i.e.: palbociclib and ribociclib. In specific, this research is divided into two phases: the first phase is a clinical retrospective observational study, and the second phase is a pharmacoeconomic analysis. Therefore, the detailed objectives of this study are as follows:

i. Phase 1: Clinical Observational Study

- To compare the clinical effectiveness of both palbociclib and ribociclib with their combinations in the first-line treatment of HR+/HER-2 metastatic breast cancer patients in Qatar through comparing the overall survival (OS) and the progression free survival (PFS) of both medications
- To investigate the effect of the different factors affecting the OS and the PFS of both of palbociclib and ribociclib with their all their indicated combinations in the first-line treatment of HR+/HER-2 negative metastatic breast cancer patients in Qatar.
- To provide a clinical insight about the safety of both medications.

ii. Phase 2: Pharmacoeconomic Study

- To generate a detailed cost-analysis of both palbociclib and ribociclib with their combinations in the first-line treatment of HR+/HER-2 negative metastatic breast cancer patients in Qatar.
- To generate a comparative cost-effectiveness analysis of both palbociclib and ribociclib with their combinations in the first-line treatment of HR+/HER-2 metastatic breast cancer patients in Qatar
- To generate a comparative cost-utility analysis of both palbociclib and ribociclib with their different combinations in the first-line treatment of HR+/HER-2 metastatic breast cancer patients in Qatar

Chapter 2: Literature Review

To confirm the novelty and the authenticity of the study objectives, thorough two systematic literature reviews would be carried out to explore if there were any similar pharmacoeconomic studies in countries with similar settings. In addition, a drug-specific pharmacoeconomic literature review about the two CDK4/6 inhibiting drugs of interest, palbociclib and ribociclib, would be conducted so that their gaps and limitations can be addressed by the present research.

2.1. Systematic Review of the Pharmacoeconomic Aspects of Breast Cancer

In the revision of the currently available pharmacoeconomic evaluations of metastatic breast cancer and taking into consideration the desire to address the local perspective of the management of metastatic disease, the author systematically reviewed the literature regarding the pharmacoeconomic part of metastatic breast cancer medications. The review scope focuses on the pharmacoeconomic analysis of breast cancer medication use in countries with developing economies, which includes the state of Qatar, GCCs, and other countries with similar economies or populations. Regarding the disease stage, to be as inclusive as possible, all the stages were included, i.e., early, advanced, and metastatic stages. Therefore, the aim of this review of the literature is to evaluate the current existing pharmacoeconomic analyses of breast cancer medications in all developing countries.

A systematic literature search was conducted in four databases: PubMed, Embase, Scopus and EconLit. Moreover, to ensure the inclusion of the gray literature or nonindexed published literature, Google and Google Scholar, theses and dissertations and conferences' abstracts were searched, and the references of all the eligible included analyses were screened. Key terms corresponding to the main domain

of pharmacoeconomics, breast cancer, medications, and developing countries were used. The keywords were classified into domains and connected with the appropriate Boolean operators corresponding to the database used. The search process covered all the articles that were published before August. 2020. Pharmacoeconomic studies were included if they were meant to address medications used in breast cancer, if they were conducted in countries with developing economies as classified by the United Nations, 2020 (14), and if they were original pharmacoeconomic evaluations. After determining the eligible pharmacoeconomic studies, the data were extracted with a predesigned data extraction tool. This extraction tool included the following parameters: authors, country, publication-related information, main outcome measures, characteristics of patients and disease, and conclusive results. In addition, pharmacoeconomic characteristics, such as study perspective, type of pharmacoeconomic approach, benefit measurement unit, discounting, and sensitivity analysis, were assessed. Based on these, the studies were assessed for their quality using the Quality of Health Economic Studies (QHES) instrument (99). This instrument is composed of a total of 16 items scored out of a total score of 100 points. As in previous health economic evaluations that used this instrument, a study is considered of a high quality if it has a score of more than 75 points, moderate if it has a score of 51 – 75, and low if it has a score of 50 and below. Other than the qualitative analysis, all statistical analyses of this review took place using SPSS Version 25. More details about the methodology of this review can be found in the published version of this review, which is available from https://www.tandfonline.com/doi/full/10.1080/14737167.2020.1794826 (100).

After screening the data sources and excluding the noneligible studies and the duplications, a total of 14 studies addressing the cost effectiveness or the cost utility of breast cancer medications in different countries were included in the final review.

Although no time limits were applied to this search, all the retrieved eligible articles were published from 2009 to 2020. Based on the setting, the included studies were from different countries as follows: three from Taiwan (101–103), two from Colombia (104,105), two from Brazil and Latin American countries (106,107), two from Iran (108,109), two from China (110,111), one from eleven sub-Saharan African countries (112), one from the Philippines (113), and one from India (114). The studies were published in different journals with different qualities. The general characteristics of the included studies are summarized in terms of the publication by author, year, country, journal where they are published, and the category of that journal in Table 1.

Table 1. General characteristics of the retrieved pharmacoeconomic studies (100)

Publication	Year	Country	Journal	Journal Category
Shih C. et. el. (101)	2009	Taiwan	PharmacoEconomics	Q1
Leung H. et. el. (102)	2018	Taiwan	Expert Review of Pharmacoeconomics & Outcomes Research	Q2
Lang H. et. el. (103)	2016	Taiwan	Journal of Medical Economics	Q2
Buendía J. et. el (104)	2013	Colombia	Biomédica	Q3
Chicaíza-Becerra L. et. el. (105)	2014	Colombia	Revista de Salud Pública	Q4
Fonseca M. et. el. (106)	2009	Brazil	Revista da Associacao Medica Brasileira	Q3
Pichon-Riviere A. et. el. (107)	2015	Seven countries from Latin America (Argentina, Bolivia, Brazil, Chile, Colombia, Peru, Uruguay)	International Journal of Technology Assessment in Health Care	Q2
Ansaripour A. et. el. (108)	2017	Iran	PharmacoEconomics	Q1
Aboutorabi A. et. el. (109)	2015	Iran	Global Journal of Health Science	Q3
Ye M. et. el. (110)	2018	China	BioMed Research International	Q2

Publication	Year	Country	Journal	Journal Category
Chen W. et. el. (111)	2009	China	Value in Health	Q1
Gershon N. et. el (112)	2019	11 African countries (Congo, Ethiopia, Guinea, Kenya, Namibia, Nigeria, Rwanda, Uganda, Zambia, Zimbabwe, and South Africa)	Cost Effectiveness and Resource Allocation	Q2
Genuino A. et. el (113)	2019	Philippine	BMC Health Services Research	Q1
Gupta N. et. el (114)	2020	India	Journal of Clinical Oncology	Q1

For the clinical classification of these studies, 10 of the retrieved pharmacoeconomic analyses focused on the drug 'trastuzumab', which is the major anti-HER-2 treatment, as a single agent or in combination with chemotherapy (103–105,107–109,111–114). Accordingly, most of the retrieved studies presented the cost effectiveness of medications used in patients with HER-2 positive expression (11 studies, those of trastuzumab and another one addressing the addition of pertuzumab to trastuzumab plus chemotherapy versus trastuzumab plus chemotherapy alone (102)). Only two studies addressed the cost effectiveness of breast cancer hormone therapy medications in HR+ patients (106,110). One study was performed to address the cost effectiveness of two specific chemotherapeutic regimens, cyclophosphamide plus epirubicin plus fluorouracil (CEF) versus CMF protocol without specifying the type of breast cancer population (101). The specific clinical settings, comparators, and pharmacoeconomic conclusions of each of the studies are summarized in Table 2.

The studies were also characterized based on their pharmacoeconomic characteristics. Regarding the perspective, nine of the cost-effectiveness analyses were

analyzed from the healthcare payer perspective (101,102,104,106–110,113), but two of them were also from a societal perspective (102,113). Three of the studies were analyzed from the third-party payer perspective (103,105,111), and two were from the societal perspective only (112,114). All the retrieved pharmacoeconomic analyses used the Markov model as their pharmacoeconomic analytical tool, but only one used net benefit regression (101). All pharmacoeconomic analyses, except for two (102,103), used patient-gained life-years (LYs) as their benefit-measuring unit. Moreover, 10 used QALYs as their primary unit for measuring the benefits (102–104,107–110,112–114). All the studies utilized discounting for both the costs and outcomes, except for one study that did not undergo discounting (101). All the studies used sensitivity analyses to ensure the robustness of their conclusion, and the majority of them, nine studies, combined both deterministic and probabilistic sensitivity analyses (102–108,110,113). The time horizon varied among the studies, but most of them were for a lifetime (104,106–108,110–114). All the studies were of a high quality, i.e., score > 75 in the QHES. The pharmacoeconomic aspects of the studies are summarized in Table 3.

Table 2. Clinical characteristics of the retrieved pharmacoeconomic studies (100)

Clinical Classification (Tumor subtype/settings)	**Publication [Author (year)]**	**Comparators**		**Study Conclusion**
		Comparator 1	Comparator 2	
All BC patients did mastectomy or lumpectomy/ Adjuvant	Shih C. (2009) (101)	Cyclophosphamide+ epirubicin+ fluorouracil (CEF)	Cyclophosphamide+ methotrexate+ fluorouracil (CMF)	CEF was not cost effective in the treatment of patients with breast cancer in Taiwan. CMF was dominant over CEF at a willingness-to-pay (WTP) threshold of $NT 1,500,000 ($US 80,000).
Hormone receptor-positive/Adjuvant	Fonseca M. (2009) (106)	Anstrazole	Tamoxifen	Anastrozole was more cost-effective than tamoxifen with an ICER of R$27,326.80/LY gained at a WTP threshold of R$29,229.00 (R$1.00 equal to US$0.40 in Brazil, 2009).
	Ye M. (2018) (110)	Aromatase inhibitor (AI), letrozole, for 5 years	Regimen 1: Tamoxifen adjuvant for 5 years Regimen 2: Tamoxifen 2-3 years then AI (letrozole to year 5)	The AI 5-year strategy with letrozole is more cost-effective than its comparators. The ICER or having an AI 5-year strategy with letrozole over a tamoxifen 5-year strategy was CNY ¥38,092/QALY gained. The ICER of 5 years of letrozole versus 2–3 years of tamoxifen and then letrozole was CNY ¥68,233/QALY gained. WTP threshold was CNY ¥171,000 (3 times GDP per capita in China, 2016).
HER2 positive/Adjuvant	Chen W. (2009) (111)	Trastuzumab adjuvant	Adjuvant docetaxel+ Doxorubicin+ cyclophosphamide	1-year adjuvant trastuzumab treatment was cost-effective across the different cities of China. The ICER ranged from US$7564 to US$7933, and US$7929/LY gained, and from US$7676 to US$8049 per QALY gained at a WTP threshold of 3 times GDP.

Clinical Classification (Tumor subtype/settings)	Publication [Author (year)]	Comparators		Study Conclusion
		Comparator 1	Comparator 2	
	Aboutorabi A. (2015) (109)	Trastuzumab adjuvant + Standard therapy	No trastuzumab (standard therapy only)	1-year adjuvant trastuzumab was not cost-effective. ICER for adjuvant trastuzumab versus no trastuzumab was US$54,223/LY gained and US$51302/QALY which are higher than the estimated Iranian WTP threshold in 2014 (10,000 to 15,000 USD).
	Pichon-Riviere A. (2015) (107)	Trastuzumab adjuvant	No trastuzumab (standard therapy only)	Trastuzumab adjuvant therapy was not cost effective compared to standard therapy in all the seven Latin American countries included in the analysis. ICER ranged from US$24,700 to US$60,800/LY gained, and from US$42,100 to US$110,300/QALY gained, at a WTP threshold of 1 GDP for each country (different thresholds in different countries).
	Lang H. (2016) (103)	Trastuzumab adjuvant + standard therapy	No trastuzumab (standard therapy only)	1-year adjuvant trastuzumab treatment was cost effective in Taiwan with an ICER of US$51,863/QALY gained at a WTP threshold of US$67,065 (2,011,950 NTD; 1 USD= NT$30 in Taiwan 2015).
	Ansaripour A. (2017) (108)	Trastuzumab adjuvant	No trastuzumab (standard therapy only)	A 6-month treatment with adjuvant trastuzumab was more cost effective than 1-year adjuvant trastuzumab versus no adjuvant trastuzumab. ICER for 1-year adjuvant trastuzumab vs no trastuzumab was €13,279/LY gained, and €16,695/QALY gained. For the 6-month adjuvant trastuzumab strategy vs no trastuzumab, ICER was €11,664/LY gained, and €14,625/QALY gained compared to a WTP threshold of €21,000 per QALY (€1 = 34,000 rials, World Bank 2011).

Clinical Classification (Tumor subtype/settings)	Publication [Author (year)]	Comparators		Study Conclusion
		Comparator 1	Comparator 2	
	Gershon N. (2019) (112)	Trastuzumab adjuvant + standard therapy	No trastuzumab (standard therapy only)	Adjuvant trastuzumab was not cost effective compared to standard therapy in the 11 African countries. The ICER ranged from US$18,709 to US$21,321/LY gained, and US$19,534 to US$21,697/QALY gained, at a WTP threshold of 1 times GDP for each of the analyzed countries (different in each country).
	Genuino A. (2019) (113)	1 year of adjuvant trastuzumab + standard chemotherapy	Standard chemotherapy alone (doxorubicin +cyclophosphamide + docetaxel)	Adjuvant trastuzumab therapy for one year was not cost effective compared to standard chemotherapy alone in the Philippines. ICER for trastuzumab was 377,009 PHP /LY gained and 453,505 PHP /QALY gained from the healthcare system perspective. From the societal perspective, ICER was 458,686 PHP/QALY. The WTP threshold in the Philippines was 120,000 PHP/QALY (1 USD = 49.9230 PHP in the Philippines in 2017).
	Gupta N. (2020) (114)	trastuzumab adjuvant+ adjuvant Chemotherapy	adjuvant chemotherapy alone (anthracycline and taxane-based drugs)	1-year adjuvant trastuzumab treatment was not cost effective in India compared to adjuvant chemotherapy alone. ICER was 156,291 INR (US$2,235)/LY gained and 178,877 INR (US$2,558)/QALY gained at a WTP threshold of 1 times GDP in 2019.
HER 2 positive/Metastatic	Buendía J. (2013) (104)	Trastuzumab + standard therapy	No trastuzumab (standard therapy only)	Adjuvant trastuzumab therapy for one year was not cost effective in Colombia. Trastuzumab ICER was US$69,701/LY gained, and US$71,491/QALY gained, which is higher than the assumed WTP threshold of US$15,000 in Colombia as per the WHO cost-effectiveness threshold of 3 times GDP per capita: US$ 15,000 in Colombia, 2010.

Clinical Classification (Tumor subtype/settings)	Publication [Author (year)]	Comparators		Study Conclusion
		Comparator 1	Comparator 2	
	Chicaíza-Becerra L. (2014) (105)	Lapatinib+ capecitabine (L+C)	Trastuzumab+ (capecitabine, vinorelbine or a taxane)	Lapatinib plus capecitabine was dominant in terms of cost effectiveness compared to its comparators at a WTP threshold of three times COL$11,216,656 (3 times GDP) with an average Colombian exchange rate in 2009 of COL$2,156 per dollar.
	Leung H. (2018) (102)	Pertuzumab + Trastuzumab and Docetaxel (TDP)	Trastuzumab and Docetaxel (TD) only	The TDP regimen was not cost effective compared to the TD regimen. The ICER was NT$18,999,687 (US$593,741) per QALY gained which is higher than the determined WTP threshold of NT$2,162,880/QALY gained in Taiwan (US$67,590, US$1=NT$32).

Table 3. Pharmacoeconomic characteristics of the retrieved studies (100)

Publication [1st Author (Year)]	**Perspective**	**P'economic Model/ Approach**	**Effectiveness Unit**		**Discounting**	**Sensitivity Analysis**		**Time Horizon**	**Quality Assessment Result (QHES scores)**
			LYs	QALY		Deterministic	Probabilistic		
Shih C. (2009) (101)	Healthcare payer (Taiwanese government)	Net benefit regression	✔	-	-	-	✔	3 years	84
Buendía J. (2013) (104)	Healthcare payer perspective (third-party payer) *	Markov Model	✔	✔	✔	✔	✔	lifetime	95
Gershon N. (2019) (112)	Societal perspective	Markov Model	✔	✔	✔	-	✔	lifetime	90
Genuino A. (2019) (113)	Healthcare system perspective & Societal perspective	Markov Model	✔	✔	✔	✔	✔	lifetime	95
Gupta N. (2020) (114)	Societal perspective	Markov Model	✔	✔	✔	-	✔	lifetime	87
Fonseca M. (2009) (106)	Private healthcare payer perspective (insurance companies, healthcare plans, health maintenance organizations and healthcare cooperatives)	Markov Model	✔	-	✔	✔	✔	lifetime	89
Pichon-Riviere A. (2015) (107)	Healthcare payer perspective (perspective of each country's healthcare system)	Markov Model	✔	✔	✔	✔	✔	lifetime	93

Publication [1st Author (Year)]	Perspective	P'economic Model/ Approach	Effectiveness Unit		Discounting	Sensitivity Analysis		Time Horizon	Quality Assessment Result (QHES scores)
			LYs	QALY		Deterministic	Probabilistic		
Ansaripour A. (2017) (108)	Healthcare perspective (Iranian healthcare system perspective)	Markov Model	✔	✔	✔	✔	✔	lifetime	90
Chicaíza-Becerra L. (2014) (105)	Third party (insurance companies)	Markov Model	✔	-	✔	✔**	✔	5 years	85
Aboutorabi A. (2015) (109)	Healthcare perspective (Iranian Health System)	Markov Model	✔	✔	✔	✔	-	20 years	99
Leung H. (2018) (102)	Healthcare payer (National Health Insurance Bureau NHBI)	Markov Model	-	✔	✔	✔	✔	5 years	92
Chen W. (2009) (111)	Third party (insurance)	Markov Model	✔	-	✔	-	✔	lifetime	96
Ye M. (2018) (110)	Healthcare perspective (Chinese healthcare perspective)	Markov Model	✔***	✔	✔	✔	✔	lifetime	99
Lang H. (2016) (103)	Third party (National Health Insurance NHI)	Markov Model	-	✔	✔	✔	✔	20 years lifetime	80

* Not mentioned but deduced from the nature of the Colombian healthcare system

** Mentioned but not clear

*** Measured life years, but the main aim was QALYs, and ICER was only calculated for QALYs

In conclusion, based on the findings of this review, a few agents and regimens of breast cancer have been addressed by pharmacoeconomics in developing countries. As a result, more pharmacoeconomic studies need to be conducted in countries with developing economies regarding more types of drug therapies for breast cancer, such as new targeted therapies and immune therapies. In addition, it was clear that most of the studies were performed among patients with the molecular subtype 'HER-2 positive', although the HR+/HER-2 subtype accounts for the majority of breast cancers (115). Therefore, more pharmacoeconomic evaluations are needed in the more common molecular subtype, as well as the other types in different stages.

2.2. Systematic Review of the Pharmacoeconomic Evaluations of the CDK4/6 Inhibitor: Palbociclib and Ribociclib

The first phase of the literature review of pharmacoeconomic evaluation of breast cancer medication in all developing countries revealed that none of the studies were found to address the pharmacoeconomics of the first-line treatment in the HR+/HER-2 negative molecular subtype of breast cancer, the most common molecular subtype. As mentioned earlier, CDK4/6 inhibitors were found to provide clinical benefit for this population of patients, which is why they were listed as a first-line treatment. Therefore, a targeted systematic literature review was performed to retrieve pharmacoeconomic assessments of palbociclib and ribociclib as first-line treatments for metastatic breast cancer worldwide.

A systematic literature search was conducted in three databases: PubMed, Embase, and EconLit. Moreover, to ensure the inclusion of gray literature or nonindexed published literature, Google and Google Scholar were searched, and the references of all eligible included analyses were screened. Key terms corresponding to the main domains of pharmacoeconomics, breast cancer, palbociclib and ribociclib

were used. The keywords were classified into domains and connected with the appropriate Boolean operators corresponding to the database used. The search process covered all the studies that were published before September 2020. Studies were included if they were meant to address the drugs of interest and if they were comparative pharmacoeconomic evaluations. However, they were excluded if they were noncomparative pharmacoeconomic studies, if they considered other types of economic analysis that did not take both the cost and outcome into consideration, such as cost analysis and budget impact analysis, or if they were not comparative or not primary (e.g., systematic reviews and commentaries). The data were extracted from the eligible articles by a predesigned data extraction tool. This extraction tool included the following parameters: authors, country, publication-related information, main outcome measures, characteristics of patients and disease, and conclusive results. In addition, pharmacoeconomic characteristics, such as study perspective, type of pharmacoeconomic approach, benefit measurement unit, discounting, and sensitivity analysis, were assessed. Additionally, the study qualities were assessed using the QHES tool.

This review included four eligible pharmacoeconomic analyses that address the issue of cost effectiveness or the cost utility of palbociclib and ribociclib from different countries. Although no time limits were applied to this search, all the retrieved eligible articles were published from 2018 to 2019. Based on the setting, the included studies were from different countries as follows: one from Spain (116), two from the USA (98,117), and one from the United Kingdom (UK) (118). The studies were published in different journals, all with high quality (Q1) as listed by Scimage, except for one study from the UK whose journal could not be found in Scimage rankings. The general characteristics of the included studies are summarized in terms of the publication by

author, year, country, journal where they are published, and the category of that journal in Table 4.

Table 4. General characteristics of the retrieved pharmacoeconomic evaluations of palbociclib and ribociclib

Publication	Year	Country	Journal	Journal Category
Galve-Calvo E. et. el. (116)	2018	Spain	ClinicoEconomics and Outcomes Research	Q1
Mistry R. et. el. (98)	2018	USA	Journal of Managed Care & Specialty Pharmacy	Q1
Zhang B. et. el. (117)	2019	USA	Breast Cancer Research and Treatment	Q1
Suri G. et. el. (118)	2019	UK	Journal of Health Economics and Outcomes Research	Not listed in SciMago

Regarding the clinical classification of these studies, all of them were based on a population of HR+ and HER-2-negative advanced breast cancer women who were postmenopausal. In addition, all of them were not based on local settings, but rather, they simulated their cohorts from different clinical trials, which were mainly the MONALEESA-2 (60), PALOMA-1 (67), and PALOMA-2 (63) clinical trials. All the studies compared the combinations of palbociclib and ribociclib only with letrozole in the first-line treatment of advanced breast cancer, but two of the studies also compared them to letrozole monotherapy (98,117). All studies identified a common conclusion that ribociclib plus letrozole was more cost effective than palbociclib plus letrozole, except for one study that concluded that both palbociclib plus letrozole and ribociclib plus letrozole combinations are not cost effective compared to letrozole monotherapy (117). However, the odd conclusion of that study can be explained by observing that

the incremental cost-effectiveness ratio (ICER) was calculated for both regimens in comparison with letrozole monotherapy, not in relation to one another, which may have increased the amount to surpass the WTP threshold. Additionally, of note, the other three studies that concluded a superiority of the cost effectiveness of ribociclib plus letrozole versus palbociclib plus letrozole are either funded by Novartis ®, the only authorized manufacturer of ribociclib, or have authors affiliated with Novartis ®; however, the affiliated authors carefully reviewed the methodology and declared no conflict of interest. All the clinical characteristics of the retrieved studies are summarized in Table 5.

Regarding the pharmacoeconomic characteristics, the studies were performed from different perspectives depending on the local settings of the studies. All the studies used a Markov model to conduct their analyses. All the studies calculated ICUR (i.e., used QALYs), but only one combined ICER and ICUR (both LYs and QALYs gained) (116). All the studies underwent discounting for costs and outcomes, except for one (118). All the studies tested their results using both deterministic and probabilistic sensitivity analyses, except for only one study that used only a one-way deterministic sensitivity analysis (117). All the studies ran their models at an appropriate time horizon from 15 years to lifetime. All the studies are of high quality, i.e., achieving a score of > 85 in the QHES instrument. The general pharmacoeconomic characteristics are summarized in Table 6.

This targeted systematic review included four pharmacoeconomic studies addressing the cost effectiveness and cost utility of palbociclib and ribociclib. Three out of the four studies concluded a superiority of the cost-effectiveness of ribociclib plus letrozole compared to palbociclib plus letrozole. However, of note, all four studies are based on simulations from the same clinical trials with the exact same patient

characteristics and outcomes, which may be a contributing factor to the similar results. However, more pharmacoeconomic studies that are based on localized settings in terms of both costs and benefits are needed from different countries.

Table 5. Clinical characteristics of the retrieved pharmacoeconomic evaluations of palbociclib and ribociclib

Publication [Author (year)]	**Population (menopausal status)**	**Comparators**			**Study Conclusion**
		Comparator 1	Comparator 2	Comparator 3	
Galve-Calvo E. et. el. (2018) (116)	Simulated from PALOMA-2 and MONALEESA-2 Trials (Postmenopausal)	Palbociclib plus Letrozole	Ribociclib plus Letrozole	-	Ribociclib plus letrozole was more cost effective than palbociclib plus letrozole from the Spanish National Health System. ICER was €1,007.69/LY gained, and ICUR was €1,543.62/QALY gained, at a threshold of 20,000 to 30,000 Euro as per the Spanish settings.
Mistry R. et. el. (2018) (98)	Simulated from MONALEESA-2, PALOMA-1, and a meta-analysis of PALOMA-1 PALOMA-2 trials (Postmenopausal)	Palbociclib plus Letrozole	Ribociclib plus Letrozole	Letrozole monotherapy	Ribocicib plus letrozole was the most cost effective among all the comparators. It dominated the palbociclib plus letrozole regimen with a cost savings of $43,037 and a gain of 0.086 QALYs compared to letrozole monotherapy and had an ICER of $210,369 per QALY compared to an acceptable threshold of $198,000 per QALY in the USA.
Zhang B. et. el. (2019) (117)	Simulation from PALOMA-1 and MONALEESA-2 trials (Postmenopausal)	Palbociclib plus Letrozole	Ribociclib plus Letrozole	Letrozole monotherapy	Neither the palbociclib plus letrozole regimen nor the ribociclib plus letrozole regimen were cost effective compared to letrozole monotherapy. Compared to letrozole monotherapy, palbociclib plus letrozole had an ICUR of $634,000 per QALY gained, and ribociclib plus letrozole had an ICUR of $440,000 per QALY gained, which at both higher than the WTP threshold of the American health system (at $100,000 per QALY gained).
Suri G. et. el. (2019) (118)	Simulation from MONALEESA-2, PALOMA-1 and	Palbociclib plus Letrozole	Ribociclib plus Letrozole	-	Ribociclib plus letrozole were more cost effective than palbociclib plus letrozole from the National Health Services (NHS) and Personal Social Services (PSS)

Publication [Author (year)]	Population (menopausal status)	Comparators			Study Conclusion
		Comparator 1	Comparator 2	Comparator 3	
	PALOMA-2 trials (Postmenopausal)				perspective in the UK at a willingness-to-pay threshold of £30 000 per QALY.

Table 6. Pharmacoeconomic characteristics of the retrieved pharmacoeconomic evaluations of palbociclib and ribociclib

Publication [1st Author (Year)]	Perspective	P'economic Model/Approach	Effectiveness Unit		Discounting	Sensitivity Analysis		Time Horizon	Quality Assessment Result (QHES scores)
			LYs	QALY		Deterministic	Probabilistic		
Galve-Calvo E. et. el. (2018) (116)	Spanish National Health System (NHS) perspective	Partitioned Survival Analysis	✔	✔	✔	✔	✔	15 years	91
Mistry R. et. el. (2018) (98)	USA private third-party payer perspective	Partitioned Survival Analysis	-	✔	✔	✔	✔	lifetime	99
Zhang B. et. el. (2019) (117)	USA Healthcare system (not clear)	Markov's Model	-	✔	✔	-	✔	lifetime	87
Suri G. et. el. (2019) (118)	National Health Services (NHS) and Personal Social Services (PSS) perspective	Partitioned Survival Analysis	-	✔	-	✔	✔	lifetime	89

2.3. Significance of the Study Findings

As per the previous literature search section ‘2.1’, there are no pharmacoeconomic studies regarding breast cancer medications either in Qatar or regionally in GCCs or the Middle East. In addition, as per the literature review section in ‘2.2’, there are only four pharmacoeconomic studies addressing the issue of the comparative cost effectiveness of palbociclib and ribociclib globally. However, none of these studies can be appropriately adapted to the Qatar setting due to the differences in the healthcare system of Qatar from these countries, the differences in the perspective from which the analysis would take place, and the differences among the economic profiles of the countries and the threshold to which the ICER and ICUR are compared. Additionally, of note, in Qatar, as per the global guidelines and the local guidelines, palbociclib and ribociclib are both used in the first-line treatment of metastatic breast cancer in combination with either an aromatase inhibitor (anstrazole or letrozole) or fulvestrant. All the current existing studies focus only on one combination, which is the combination of these CDK4/6 inhibitors along with letrozole only. Therefore, there should be a more thorough pharmacoeconomic analysis of all possible combinations in first-line treatment. Last, these studies are based on economic modeling on the basis of the same prospectively collected clinical trial data (from MONALEESA-2, PALOMA-1, and PALOMA-2 trials); this type of economic modeling is often associated with uncertainty in input parameters, which reduces the clarity of conclusions and often needs to be tested by many sensitivity analyses (119). In addition, since these pharmacoeconomic analyses are based on the same clinical trials, their cohorts had the same clinical characteristics, so they were all postmenopausal. Nonetheless, ribociclib is indicated for all menopausal stages (premenopausal, perimenopausal, and postmenopausal), and palbociclib is indicated for postmenopausal women, as explained earlier in ‘1.3.2.3.3’, so all of these subclasses of patients need to be included in the

pharmacoeconomic analyses to ensure fair generalizable decision criteria regarding first-line therapy. As a result, all of these gaps in the current existing literature should be addressed by a thorough pharmacoeconomic analysis of the authorized CDK4/6 inhibitors that is based on data from local settings in Qatar.

The significance of this study lies in the fact that it would be the first local study that addresses the pharmacoeconomic analysis of the two CDK4/6-inhibiting medications with their combinations in the first-line treatment of HR+/HER-2-negative metastatic breast cancer patients. Locally, cancer is a well-established challenge in Qatar that was chosen as a major research topic in the Qatar National Research Strategy (QNRS), and breast cancer was at the top of all cancers (120). Therefore, the findings of this research will directly serve the QNRS mission and would be utilized by stakeholder decision makers to inform them about the inclusion/exclusion of palbociclib and/or ribociclib in the NCCCR formulary not only based on the existing clinical evidence but also based on local cost-effectiveness evidence that also addresses the gaps of previous existing literature. In addition, the findings of this study can be used regionally by countries that have similar economic profiles, healthcare systems, and similar populations to Qatar, such as some GCCs and Middle Eastern countries, since this research is considered novel to the region. Internationally, the findings of this research can also be used if a country has a similar healthcare system and similar pharmacoeconomic considerations to Qatar. This is because the population in Qatar is diverse and is not based solely on Qataris, and this will be the first study based on realistic data from local settings, not based on the available clinical trials, such as the existing evidence.

Chapter 3: Methodology

This study is divided into two sequential phases. As mentioned earlier, the first phase was a clinical study concerning the efficacy and safety of palbociclib and ribociclib in Qatar. Whereas phase two was to generate a through pharmacoeconomic analysis of both medications. The detailed methodology of each phase is indicated in this chapter in detail.

3.1. Phase 1: Clinical Phase

3.1.1. Settings.

This is a retrospective observational study that is based on retrospective data collection from patients' medical records from the NCCCR. The NCCCR is the only national cancer specialized hospital in Qatar that provides medical care related to cancer and other serious blood-related illnesses (such as thalassemia and amyloidosis) to both Qatari citizen, and non-Qatari residents in Qatar. As mentioned earlier, it is a governmental non-profit organization that provides the cancer care treatment to all patients for free. It is a tertiary level hospital and it compromise on of the nine major hospitals of HMC in Qatar.

3.1.2. Ethical approval.

Prior the actual start of this study, the study was firstly ethically approved from the Medical Research Center (MRC) at Hamad Medical Corporation on January 30, 2020 under the protocol approval number: MRC- 01-19-318. The approval letter from the MRC is inserted in Appendix.1. In addition, this study is approved from the Qatar University International Review Board (QU-IRB) on February 10, 2020 under the approval number: QU-IRB- 1231- E/20. The approval letter from the QU-IRB is

attached in Appendix.2. There was no need for an informed consent as the data was collected retrospectively from the medical records without in-person interaction with patients.

3.1.3. Population and sample.

As mentioned earlier in the study objective section '2.5', this study is concerned with the evaluation of the cost-effectiveness and the cost-utility of the two medications 'palbociclib' and 'ribociclib' with their FDA approved combination in the treatment for stage IV metastatic breast cancer. Therefore, in correspondence of this goal, a retrospective data collection for all the patients receiving either of the two treatments is conducted from January 2017 to December 2019. Due to the retrospective nature of this study, the sampling method is 'sampling by convenience' where all the medical records for patients who received either palbociclib or ribociclib in the specified data collection period will be included if they are eligible. Patients' eligibility in the study is determined according to predetermined inclusion and exclusion criteria as follows.

Inclusion criteria:

- Being a female breast cancer patient with stage IV (advanced or metastatic breast cancer disease as consistent with the FDA indicated population for CDK4/6 inhibitors).
- Having the cancerous cells to be hormonal receptor positive for either both estrogen and progesterone (ER+ and PR+), or hormonal receptor positive for only estrogen receptors (ER+, PR negative). The status of hormonal receptors of cancer cells is often determined by immunohistochemistry methods and is assumed to positive if at least 1% of the cells examined have estrogen and/or progesterone receptors.
- Having HER-2 negative cancerous cells. Similarly, the HER-2 status is often

determined by immunohistochemistry or by Fluorescence In-Situ Hybridization (FISH). An immunohistochemistry result of 0 to 1 means a weak representation of HER-2, whereas a score of 2 means a borderline, and a score of 3 means a positive HER-2 (121).

- Receiving appropriate combination with the treatments of comparison as approved by the FDA; i.e.: receiving palbociclib with either AI (anstrazole or letrozole) or fluvestrant or receiving ribociclib with either AI or fluvestrant or tamoxifen.
- Having a corresponding menopausal status to the treatment of interest according to the FDA. I.e.: being ONLY postmenopausal while firstly receiving palbociclib with its selected combination (either naturally or by ovarian suppression by oophorectomy) or being premenopausal or perimenopausal or postmenopausal when receiving ribociclib with its selected combination.
- Completing at least three cycles of the FDA indicated treatment of palbociclib with its combinations or ribociclib with its combinations.

Exclusion criteria:

- Being a male patient with breast cancer, even if the patient is a stage IV patient, and meeting all the other inclusion criteria.
- Having cancer hormonal receptor and HER-2 status that is not corresponding to the ones included in the inclusion criteria, i.e.: triple positive, triple negative, or PR+ and ER negative breast cancer.
- If a patient is receiving a non-FDA indicated combination with the treatment of interest (e.g.: receiving tamoxifen alongside with palbociclib).
- Receiving a treatment with a non-corresponding menopausal status, i.e.: receiving palbociclib while still be premenopausal or perimenopausal.

- Not completing at least three cycles of an appropriately indicated treatment of either of the two agents.
- Receiving one of the CDK4/6 inhibitors as a second line after developing a disease progression on another CDK4/6 inhibitor, e.g.: receiving a palbociclib combination as a second line treatment after a patient has developed a disease progression using a ribociclib combination.

3.1.4. Outcome measures.

The two treatment groups (palbociclib and ribociclib) will be evaluated for primary and secondary outcome measures as follows:

Primary outcome measures:

- Overall survival (OS) duration in months. The OS in general is defined as the time for which a patient survives with the disease but without dying due to a disease worsening, treatment side effect, or any other cause of death (122). In the context of this research, it is the time in months that a patient lives for from the point of receiving one of the two treatments (palbociclib or ribociclib) till death, due to a progressed disease, side effect, hospitalization, or any other cause of death.
- Progression-free survival (PFS) duration in months: it is the time in months that a patient survives without developing a further progression or further metastasis of her cancer condition (123). The documentation of progression is often very clear in the patients' medical files, either by radiology, or by clinical visits, or by both. Of note, the duration of living with a progressed disease can then be also calculated which is equal to OS minus PFS.
- Death: it is the end of life of a patient either due to treatment side effect, due to new progression, or due to any other cause of death.

Secondary outcome measure:

- Adverse drug reactions (ADRs). In referral for the definition of ADRs, they are the undesirable events that happens when medications are taken as indicated (i.e.: at the indicated dose, frequency, and route of administration, unlike side effects which refer to all the undesirable events that can happen while taking medications whether a medication is taken as indicated or not (124). Therefore, the ADRs of interest in this research included blood related adverse drug reactions such as: neutropenia and febrile neutropenia, anemia, thrombocytopenia, and pancytopenia. In addition, they include gastric related side effects such as diarrhea, constipation, nausea and vomiting, and abdominal pain; cardiac side effects such as corrected QT interval prolongation (QTc prolongation); neuropathy and fatigue, and impaired liver functions.

3.1.5. Data collection and handling.

As mentioned earlier, in this retrospective study where secondary data were collected from the patients' medical records from the CERNER®, which is online health information technology system used in all HMC hospitals, including the NCCCR. The data collection period is from January 2017 to December 2019. The collection of data is stopped at the end of 2019 due to the MRC ethical policy which restricts the data collection not to be after the date of getting the approval. All patient records are retrieved from the system based on the medications of interest (palbociclib and ribociclib) intake. The list was ordered based on the dispensing date of the medications of interest, so duplicated patients were removed, and data were rearranged and coded based on the patient healthcare (HC) number. Due to the confidentiality and the signed data-share agreement, HC numbers and related patient's

specific data could be accessed only by the master's student, primary investigator from HMC, and primary investigator from the university side.

Data collection was based on a predetermined data collection tool to meet the objectives and the primary and secondary outcome measures. The major parameters in this data collection are: patient characteristics, menopausal status, hormonal receptors and HER-2 status, whether a patient diagnosis of metastatic breast is de novo (first time ever to be diagnosed with breast cancer) or recurrent after previous breast cancer diagnosis, whether a patient has received a prior hormonal therapy before the CDK4/6 inhibiting drugs of interest or not, the name of the CDK4/6 inhibitor used for a patient with the dose and the combination, the date a patient firstly received one of the two drugs of interest, the date a patient discontinued the drug of interest (if applicable), the reason of discontinuation (if applicable), and the date a patient developed further disease progression (if applicable). In addition, the number corresponding lab tests both before progression (if any), and after progression (if any) were collected. These include number of complete blood count (CBC) lab tests, number of comprehensive metabolic panel (CMP) lab tests, number of liver function tests, number of endocrinology related lab tests (e.g.: vitamin D, vitamin B, TSH and FSH levels), number of tumor markers and catechol amine tests, number of coagulation lab tests (PT, PTT, INR). Moreover, the corresponding clinical imaging and their counts for both the period before and after progression (if applicable) were collected. The clinical imaging of interest was: Magnetic resonance imaging (MRI), computerized tomography (CT) scan, x-ray, ultrasound, mammogram, and the dual-energy X-ray absorptiometry (DXA) for bones. Besides, due to the reported possible cardiac side effects, the number of cardiac electrocardiogram (ECG or EKG) records, and echocardiogram scans are documented. Lastly, the date of death of patient (if

applicable) was documented.

3.1.6. Statistical analysis.

Descriptive statistics were used to describe the main patients' demographic characteristics which include nationality, age, menopausal status, hormonal receptors and HER-2 status, metastasis diagnosis status, and prior receive of hormonal therapy status. Means with standard deviations or medians with quartiles along with the percentages would be used depending on the type of data distribution. The normality of the data would be tested using Shapiro-Wilk test. The data are claimed to be normally distributed if they have a p-value that is more than 0.05 based on the Shapiro-Wilk test. In addition, descriptive statistics were used to summarize the number of cycles completed at the two treatment groups (palbociclib and ribociclib), the number of patients who experienced side effects, the hospitalization and the overall hospitalization.

In correspondence of the primary outcomes, two simple time to event survival analyses using Kaplan-Meier estimate would be used; one is regarding the OS and the other one is for the PFS. Data would be classified in accordance to three major categories: time of the total follow up, outcome (developing the event or censored, i.e.: did not develop the event of interest during the follow period), and treatment group (palbociclib or ribociclib groups). For the OS Kaplan Meier estimate, the event of interest is claimed to be death. Whereas, for the PFS Kaplan Meier estimate, the event of interest is claimed to be developing a new disease progression. For both Kaplan-Meier analyses, the follow up time is the duration in months starting from the date a patient received either palbociclib or ribociclib to the date a patient developed the event of interest (either death or progression depending on the event of interest in the curve) or the end of follow up period (end of 2019 in case a patient is censored).

It is noteworthy that by using this Kaplan-Meier estimator, there are three by-default assumptions related to data (125):

1. All patients have the same survival probabilities regardless the time they entered the study for follow up.
2. Patients who are censored, have the same survival prospects of those who are continued to be followed up. That means that the censoring is independent from developing the outcome of the event of interest (i.e.: from developing death or a new progression).
3. The event (either death in case of OS survival analysis, or progression in case of PFS survival analysis) is to occur at follow up period.

To test the survival distribution of the two curves (OS and PFS curves) for the two treatment groups (palbociclib and ribociclib), log-rank test would be used. The log-rank test is a non-parametric test that is used to test the differences of the survival curves in time-to-event analyses such as Kaplan Meier estimator. It has a null hypothesis there is no difference between the two groups in terms of survival. Therefore, the two treatment groups would be considered to have a statistically significant difference in the survival distribution (either in PFS or OS) if the p-value of the log rank test is less than 0.05. After this, the Kaplan Meier tables, plots, and survival functions would be obtained, and further used for the modeling as will be detailed in the next section (3.2). To explore what the factors affecting the OS and the PFS are, a COX regression analysis was performed. The independent variables entered in the COX-regression analysis were nationality, menopausal status, recipient of a previous hormonal therapy, diagnosis of metastasis (de novo or recurrent), site of metastasis, and the combination medication(s) with the CDK4/6 inhibitors. All the statistical analysis is compared to a significance level of 0.05 and conducted using the

Statistical Package for the Social Sciences (SPSS)® version 26 (126).

3.2. Phase 2: Pharmacoeconomic Analysis

3.2.1. Cost analysis of CDK4/6 inhibitors.

A comprehensive cost analysis of the components of the CDK4/6 inhibitors intake treatment period were analyzed in detail. That is, for each of the two available CDK4/6 inhibitor medications, palbociclib and ribociclib, all the treatment components were analyzed and based on accounting methods to yield a comprehensive cost analysis. For the PFS, the cost analysis included the following components: the CDK4/6 inhibitor drug acquisition cost, the combination drug acquisition cost, laboratory tests needed throughout the treatment period [complete blood count (CBC), blood chemistry tests (comprehensive metabolic panel, liver function test, magnesium and phosphorus levels), endocrinology tests (25-hydroxyvitamin D, TSH receptor antibody, Follicle stimulating hormone, vitamin B12), tumor markers and chatechol amines (thyroglobulin, and carcinoembryonic antigen, CEA), coagulation tests, and urine analysis test. In addition, the clinical radiology components including: X-ray, ultrasound, mammogram, magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography scan (PET scan), and the bone density DEXA scan were included in the comprehensive cost analysis. Besides, the required cardiac procedure for the CDK4/6 inhibitors which are the electrocardiogram (ECG), and the echocardiogram were analyzed in the cost analysis. Lastly, the costs of the outpatient visits and the hospitalization visits were included in the model. For all these inputs, the costs were obtained from the HMC formulary from the department of finance and accounting for the financial year 2019/2020, except for the costs of outpatient visits and the hospitalization cost which were estimated by clinical experts. For the number of

consumed units during the CDK4/6 inhibitors, they were summarized from the data collected in phase 1. The overall costs mean rank between palbociclib and ribociclib were calculated using Mann-Whitney test due to the assumption of non-normality distribution of the overall costs as confirmed by Kolmogorov-Smirnov test. In addition, the detailed average total unit consumption costs per patient per course of treatment and the total estimated cost per course of treatment were calculated.

To take a further step in the analysis, we studied the effect of the different baseline characteristics (independent variables) on the overall cost of the CDK4/6 inhibitor medications. The following independent variables were entered in the analysis: age, nationality, menopausal status, recipient of a previous hormonal therapy, diagnosis of metastasis (de novo or recurrent), the site of metastasis, and the recipient of previous hormonal therapy. The cost data were assumed to be not normally distributed and tested for this assumption using Kolmogorov-Smirnov test. Based on this assumption, a generalized linear model (GLM) was chosen to test the effect of the independent variables on the overall cost of the two medications with the tested variables assumed to be non-normal, following a gamma distribution with a link log function. A generalized linear model is an extension of the general linear model when the assumption of normality is violated to predict the relationship between one non-normally distributed dependent variables and one or more independent variable(s) (127). Running the GLM, a goodness of fit chi-square was generated to explore the fitness of the overall model. In addition, omnibus test was run to compare the fitted model against the intercept-only model. The overall model effects and parameters were also investigated. All the statistical analysis was conducted on SPSS ® with a two-tailed significance level of 0.05.

For the progressed disease status, both treatment strategies were assumed to

have the same cost of progression since patients are managed similarly after progression as per the international guidelines. Therefore, same components of cost analysis were included in the PD health status which were: the most common three chemotherapeutic regimens used [Capcitabine, CMF protocol (cyclophosphamide, methotrexate, fluorouracil) or AC protocol (doxorubicin cyclophosphamide), and eribulin)], the most common first and second line hormonal therapies used (everolimus + exemestane, and fluvestrant), laboratory tests needed throughout the treatment period [complete blood count (CBC), blood chemistry tests (comprehensive metabolic panel, liver function test, magnesium and phosphorus levels), endocrinology tests (25-hydroxyvitamin D, TSH receptor antibody, Follicle stimulating hormone, vitamin B12), tumor markers and catechol amines (thyroglobulin, and carcinoembryonic antigen, CEA). Also similar to the PFS health state costs, the clinical radiology components were analyzed, which were: X-ray, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography scan (PET scan). In addition, the required cardiac procedure for the follow up during the progressed disease state which are the electrocardiogram (ECG), and the echocardiogram were analyzed in the cost analysis. All of these costs were also retrieved from the department of accounting and finance from HMC. Lastly, the costs of the outpatient visits and the hospitalization visits were included in the model, but they were estimated based on HMC clinician collaborator's opinion.

3.2.2. Cost-effectiveness and cost-utility analyses of CDK4/6 inhibitors.

3.2.2.1. Perspective and threshold.

The aim of this pharmacoeconomic analysis was to evaluate the cost-effectiveness of the two CDK4/6 inhibitors treatment strategies, palbociclib and

ribociclib with their indicated combinations, from the healthcare payer perspective, Hamad Medical Corporation- NCCCR. Therefore, only the direct medical costs were included, with no consideration to other types of costs such as direct non-medical costs or intangible costs.

As for the willingness-to-pay (WTP) threshold, both of the treatment regimens were compared for their incremental cost-effectiveness and incremental cost-utility to a WTP of less than three times the national annual gross domestic product (GDP) per capita as per the World Health Organization (WHO) for cost-effective interventions (128). In addition, they were compared to a WTP threshold of one GDP as per the WHO recommendation for a very cost-effective intervention (128). As a result, a treatment regimen of an incremental-cost of less than 576,150 QAR per QALY gained is considered to be cost-effective and very cost-effective if it is less than 192,050 QAR per QALY, based the Qatari GDP/ capital of 52,751 USD (1 USD = 3.65 QAR, 2020 financial year) (129) .

3.2.2.2. Model structure.

To estimate the cost effectiveness and cost-utility of palbociclib and ribociclib treatment regimens in the first line treatment of HR+/HER-2 negative stage IV breast cancer patients in Qatar, a Markov decision analytical model was developed based on the individual patients' data obtained through the first phase of the project as well as published phase III randomized controlled trials data on treatment strategies effectiveness, patients' quality of life, resource utilization and resources utilization cost. The model is constructed of three health states: progression free disease, progressed disease, and death. All patients were assumed to enter the model in the 'progression free disease' state and they were evaluated for their health state at the end of each Markov cycle. The transition between the health states follows a unidirectional

transition, where at the end of each cycle, a patient can stay in the same status or move to the next status or move directly to death (the absorbing status), with no back transition to the previous status. The Markov cycle length is assumed to be one month since it is the normal evaluation for the event development as per the clinical guidelines. A visualization of Markov's model for this study is illustrated in Figure 3. Of note, to overcome any over-estimation, the model was corrected based on a within-cycle-correction (WCC). WCC is mathematical correction that makes the calculations of costs and effectiveness values of a specific health state relying on the average percentage of the cohort at the beginning and the end of each cycle, providing a more accurate estimation for costs and effectiveness values (130). The model was developed and analyzed using the TreeAge Pro 2020 ® software. The real visualization of the model with its full inputs is provided in Appendix 3.

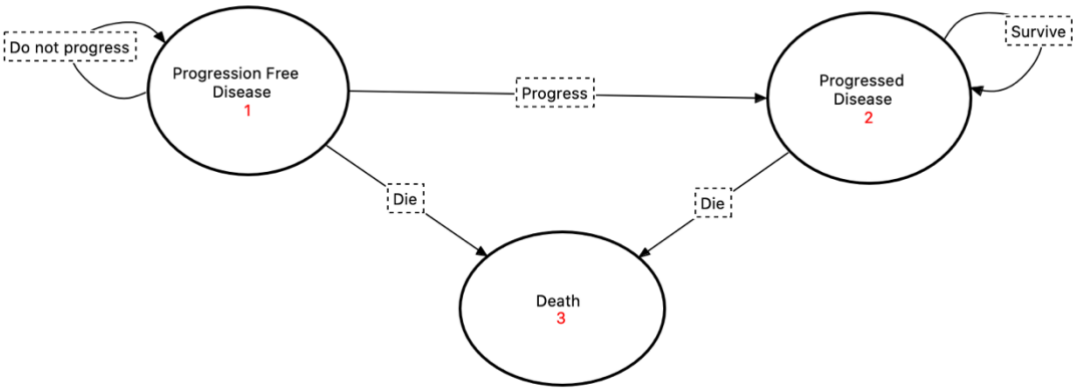

Figure 3. Visualization of the Markov's model implemented in the study with the state diagram and their transitions' pathways

3.2.2.4. Model outcomes.

The aim of the model was to create a comprehensive estimation of the overall cost associated with palbociclib and ribociclib treatment strategies, as well as their overall effectiveness estimation over a time horizon of 10 years. Based on the total estimated cost and effectiveness of both strategies, the ICER would be calculated and the cost per QALYs would be compared to the pre-specified threshold of cost-effectiveness to conclude the decision of effectiveness or not. The ICER would be calculated as per the below Equation 1 (131).

$$ICER = \frac{Cost\ of\ Ribociclib\ (QAR) - Cost\ of\ Palbociclib\ (QAR)}{Ribociclib\ effectiveness(QALYs) - Palbociclib\ effectivness\ (QALYs)}$$

Equation 1. Incremental cost-effectiveness ratio equation

The two interventions were separately evaluated for their cost-effectiveness based on the pre-specified threshold. As mentioned earlier, an intervention would be considered cost-effective if the total cost/ QALY gained is less than 576,150 QAR, and very cost effective if the total cost/QALY gained is less than 192,050 QAR per QALY. In addition, the incremental-cost effectiveness ratios were compared to the same threshold for the decision-making purpose.

3.2.2.5. Model inputs.

The model inputs included costs, transition probabilities between health states, and effectiveness (utilities). These were estimated based on individual patients' data and based on published literature to feed the model as follows:

- Costs

  The costs included for the model were costs per patient per month for health states for each of the treatment strategies. The detailed cost analysis for each

health state for each strategy were explained earlier in 3.2.1. As mentioned earlier, all costs were based on the 2019/2020 financial year. All costs were calculated in the local currency, Qatar riyals where 1 USD = 3.65 QARs. All the costs and the other model input parameters are summarized in Table 7 below.

- Effectiveness-based transition probabilities

  Transition probabilities are of the most important Markov's inputs that express the likelihood of the transition of the cohort between the different health status over the different Markov cycles. They are usually expressed in percentage between 0% to 100% or in fractions between 0.0 to 1.0 (131). For this study, the transition probabilities were calculated from the real individual patient data based on the first phase (clinical phase). That is, firstly the cumulative probability of each of the events of interest for the two comparators were calculated based on Equation 2, where *P* is the probability and A is the event of interest. Secondly, the cumulative probabilities were converted into a rate as per the below Equation 3, where p is the cumulative probability, *r* is the rate, and *t* is the time in years (131). Lastly, the rate was converted back to 1-month transition probability as per Equation 4 (131).

$$P\ (A) = \frac{Total\ number\ of\ cohort\ with\ event\ (A)}{Total\ number\ of\ cohort}$$

Equation 2. Cumulative probability of event (A) for a patient cohort

$$r = -\frac{\ln(1 - P)}{t}$$

Equation 3. Constant rate from probability

$$Time\ probability\ (A) = 1 - \exp\ (-r\ t)$$

Equation 4. Fixed time probability

The three prior equations were applied to both the palbociclib treatment arm, and ribociclib treatment arm, generating three unique transition probabilities with two complimentary ones for each arm as follows: monthly transition probability from PFS to PD, monthly transition probability from PFS to death, their complementary probability of staying in the PFS, monthly transition probability from PD to death, and its complimentary monthly probability of staying PFs for both groups. A demonstration of the monthly transition probability calculations for PFS to PD for palbociclib group is illustrated in Appendix 4. All the transition probabilities and other model input parameters are summarized in Table 7.

- Utilities

  Quality of life was used to investigate the impact of the quality of life (QoL) on every additional year gained by the treatment of palbociclib and ribociclib to generate what is called, quality adjusted life years (QALYs). Due to the retrospective nature of the first phase of the study where patient's data were collected from pre-existed patient records, we could not conduct a QoL study to measure the patient's health related quality of life (HRQoL). Therefore, the QoL values were obtained from the published literature (132–134). For the palbociclib group, the QoL values for the PFS health state were summarized from published literature from findings from the PALOMA-2 trial, which is the largest phase III trial regarding palbociclib. In this publication, they used different measurements for QoL, but the EQ-5D VAS results of QoL were used for this

pharmacoeconomic analysis (132). It revealed that the mean overall study score for QoL for the palbociclib arm was 0.7507 (73.87–76.27) (132). On the other hand, for the PFS for the ribociclib arm, it was obtained from the published QoL results from the MONALEESA-3 trial, a phase III RCT that compared ribociclib plus fluvestrant to placebo plus fluvestratn. Therefore, the same quality of life value was awarded for the PFS states in both palbociclib and ribociclib groups. Therein, they used European Organization for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC-QLQ-C30) to assess the quality of life for the patients on a 1-100 scoring scale. The mean (SD) EORTC-QLQ-C30 score for the ribociclib arm towards the end of treatment before progression was 71.0 (18.5), yielding a quality of life value of 0.710 that was used for this analysis (133). Lastly, for the progressed disease status, it was assumed that there was no difference in terms of the quality of life between palbociclib and ribociclib due to the similar management. Therefore, the same utility value of 0.45 was used as per a published literature systematic review (134). All utility values, and other model inputs, are summarized in Table 7.

Table 7. Inputs of the Markov's model

Model Input	**Value**	**Minimum**	**Maximum**	**SD**	**Resource**
Median Health States Costs/ Months (QAR)					
PFS (Palbociclib)	11,628.5	7,477.4	14,316.4	-	Individual patient Data (see 3.2.1)
PFS (Ribociclib)	10,258.1	8926.4	11,054.2	-	Individual patient Data (see 3.2.1)
PD	2,942.6	1,893.9	4,118.3	-	Individual patient Data (see 3.2.1)

Model Input	Value	Minimum	Maximum	SD	Resource
Utility Values					
PFS (Palbociclib)	0.7507	0.7387	0.7627	-	(132)
PFS (Ribociclib)	0.710	-	-	0.185	(133)
PD	0.45	-	-	-	(134)
Monthly Transition Probabilities					
PFS to PD (Palbociclib)	0.0459708	-	-	-	Individual patient Data (see 3.1)
PFS to death (Palbociclib)	0.0005916	-	-	-	Individual patient Data (see 3.1)
PD to death (Palbociclib)	0.0116347	-	-	-	Individual patient Data (see 3.1)
PFS to PD (Ribociclib)	0.0588690	-	-	-	Individual patient Data (see 3.1)
PFS to death (Ribociclib)	0.0029835	-	-	-	Individual patient Data (see 3.1)
PD to death (Ribociclib)	0.0063706	-	-	-	Individual patient Data (see 3.1)
Discounting Rate					
	3.5%	1.5%	3.5%	-	(135)

3.2.2.4. Discounting.

Although there is no specific recommended discounting rate for costs and outcomes in Qatar, discounting was applied to the model as per the international guidelines. The discounting rates varies between the different countries in the world, ranging from 1.5% to 7% in most of the European region and USA. In our model, we followed the UK recommendation for the discounting rate of 3.5% for both costs and effectiveness outcomes (135).

3.2.2.5. Sensitivity analysis.

To address the impact of any uncertainties regarding the model inputs on the

conclusion of the cost-effectiveness or cost utility, a univariate deterministic sensitivity analysis was implemented. Cost was the first deterministic parameter that was assessed by the sensitivity analysis. As per the previously listed table 7, costs of PFS and PD for both arms were assessed for uncertainty by applying +/- 20% variation in their value as per the general recommendation of cost variation in the deterministic sensitivity analysis (136). Transition probabilities were also an important model input that needed to be addressed for uncertainties since it was primarily obtained from the individual patient data. Therefore, the transition probability from PFS to PD of the palbociclib group was obtained from the PALOMA trial (64), where it indicated that 128 patients out of the 347 patients have developed progression throughout a median follow up period of 8.9 months. The cumulative probability was calculated and converted to a monthly probability as per equations 1, 2 and 3 above, yielding a monthly probability of 0.0503. This monthly probability was entered in the upper range value of the sensitivity analysis accordingly, and the case-base value was considered the lower range value. Regarding the uncertainty of the transition probability of PFS to PD in the ribociclib group, it was estimated from the MONALEESA-2 trial (60). As per the MONALEESA-2 trial, the 12-months PFS was 72.8% [95% CI (67.3% - 72.6%)]. Therefore, the PD rate was calculated and converted to a monthly probability as per the previously listed equations 2 and 3. This yielded a 0.0261 [95% CI (0.021- 0.325)] that was used in the sensitivity analysis. Lastly, for the utility values, the minimum and maximum utility ranges were used when available, the standard error was also used when provided. If both were not provided, the utility values were varied by 20%. Of note, the probabilities of death (PFS to death and PD to death) in both treatment arms were not included in this sensitivity analysis. This is because that the probability of PFS to death in both

treatment arms was too low to be assumed as a major affecter on the results if there were uncertainties. Moreover, the death outcome in the major phase III published trials (MONALEESA and PALOMA trials) was not the primary outcome, so it is uncertain to rely on their results to be included for this sensitivity analysis and draw conclusion. Therefore, only the previously listed eight parameters were used in this sensitivity analysis. All univariate sensitivity analyses were calculated at 10-timepoint intervals using TreeaAge Pro® software. The sensitivity analysis inputs and outputs are summarized in the results section in table 16.

Probabilistic sensitivity analysis (PSA) was also implemented. The basic concept of PSA is similar to the deterministic one. That is, it investigates the impact of the uncertainty related to model inputs on the outputs. Nonetheless, unlike the deterministic sensitivity analysis, it focuses on the impact of combined uncertainties of the multiple inputs together to assess the robustness of the overall confidence in the case base conclusion. Monte-Carlo simulation was used to conduct the PSA (86,136). In Monte-Carlo simulation, the variables are inputted as distributions rather than just fixed values and the different distributions of the different variables are inputted together generating a large number of scenarios with possible outcomes (86). The large number of the scenarios is then aggregated and compared to the original base-case result to test the robustness of the case-base conclusion. Similar to the deterministic sensitivity analysis, the same eight input factors were considered for the PSA (86). Regarding the distributions of the factors, costs were given a gamma distribution, and probabilities and utilities were given a beta distribution. For the costs, the mean costs were used with their SD as estimated from the real individual patient data. For the probabilities, the base-case probabilities were re-calculated based on the minimum and maximum follow up period, and the mean and SDs were also used to

estimate the gamma distribution parameters. Similarly, for the utilities, the mean and the SD were used. For the PFS utility in the palbociclib arm, the SD was calculated from the provided 95% confidence interval using equation 5 listed below (137). For the PFS utility in the ribociclib treatment arm, the study had provided the SD (18.5%). For the PD utility value, the 95% CI ranges were not accessible nor was the SD, therefore, the SD was assumed to be of a 20%. The detailed distributions types and distribution inputs for the parameters included in the probabilistic sensitivity analysis are summarized in Table 8. The Monte-Carlo simulation analysis was run to yield 10,000 different scenarios. The cost-effectiveness (CE) scatter plot was generated to present all the 10,000 different model calculations on the same axes of cost and effectiveness to give a demonstration about their cost-effectiveness. In addition, the incremental cost-effectiveness plot (ICE) was generated to illustrate the ratio of the generated simulated calculations favoring ribociclib treatment versus palbociclib treatment, and the overall confidence of the base-case conclusion was reported accordingly. Lastly, to investigate the impact of the change in the WTP on the cost-effectiveness conclusion of the two treatment strategies, a CE acceptability curve was generated.

$$SD = \frac{\sqrt{N}(upper\ limit - lower\ limit)}{3.92}$$

Equation 5. Calculating the standard deviation (SD) from the 95% confidence interval

Table 8. Probabilistic sensitivity analysis inputs

Input	Distribution	Point Estimate	Standard Deviation
Cost of PFS State for Palbociclib (QAR)	Gamma	11,628.515	6,838.95

Input	Distribution	Point Estimate	Standard Deviation
Cost of PFS State for Ribociclib (QAR)	Gamma	10,285.092	2,127.73
Cost of Progressed Disease state (QAR)	Gamma	2,942.6	2,224.34
Monthly Probability for PFS to PD in Palbociclib	Beta	0.04597	0.01364
Monthly Probability for PFS to PD in Ribociclib	Beta	0.05887	0.0260
Utility of PFS State for Palbociclib	Beta	0.75	0.1290
Utility of PFS state for Ribociclib	Beta	0.70	0.185
Utility of Progressed Disease State	Beta	0.45	0.20

Chapter 4. Results

In this chapter, the study findings will be presented in detail. Herein, the findings are divided into two subsections to follow the same sequence of the research implementation. Therefore, they will be illustrated as: the results of the clinical phase, and the results of the pharmacorconomics phase.

4.1. Results of Phase 1: Clinical Phase

A total number of 145 potentially eligible patients' records were identified for screening at the period from 01.01.2017 to 31.12.2019. Out of the 145 total retrieved records, 39 records were excluded due to not meeting the inclusion/ exclusion criteria as follows. To detail, 12 records were excluded because patients were not eligible based on the menopausal status, i.e.: patients were receiving palbociclib where they are either still premenopausal or perimenopausal without undergoing a total oophorectomy. In addition, five other medical records were excluded due to have different sub-molecular type based on the receptors and proteins status, i.e.: being triple positive breast cancer (n=3), or being triple negative breast cancer (n=1), or being positive for the PR and not the ER (n=1). Moreover, two more medical records were excluded for not being on an approved FDA combination with the indicated CDK4/6 inhibiting agent; one was based on a patient receiving palbociclib in combination of both letrozole and fluvestrant simultaneously, and one was based on a patient receiving ribociclib in combination with exemestane. Lastly, the failure of the completion of the minimum number of cycles (3 cycles) leaded to the exclusion of 18 medical records. Therefore, the total final eligible patients' records were 108 that included in the analysis of this study is 108 medical records based on exclusive 108 patients.

As per the study inclusion/ exclusion criteria, all the included patients were females. The average age of the population was 55.92± 10.59 years, with a median (IQR) of 55.00 (16) years. The population were from different races as follows: Arabs (n= 80; 74.1%), Asian (n= 13; 12%), Europeans (n= 11; 10.19%), South African (n=2; 1.9%), and South American (n=2; 1.9%). Most of the patients were considered overweight with a median body mass index (BMI) of 29.46 (IQR= 8.14). In addition, as per the inclusion/ exclusion criteria, all patients needed to be hormonal receptor positive and HER-2 negative; the majority of the patients were ER+ PR+ HER-2 – (77.8%), whereas the rest were ER+ PR – HER-2 –. None of the patients were of ER– since they were excluded from the beginning. For the diagnosis of the metastasis, 63.9% of the patients received their diagnosis as a recurrent or progressive disease, whereas the rest of the population had it 'de novo'. Bones were the most common site for metastasis accounting for 36.1% of all the cases. Most of the patients received hormonal therapy before prior to their first receive for the CDK4/6 inhibitor drug, with 55.6% of them in the adjuvant setting and 25.9% of them in the metastatic settings. Of those who received hormonal therapy in the adjuvant settings, most of them were resistant to hormonal therapy, meaning that they developed recurrence/ metastasis while taking the hormonal therapy without completing the indicated period (26.9%). On the other hand, the majority of the patients who received hormonal therapy in the metastatic setting, 15.7% of the 25.8% who received it in metastatic setting, received only one-line hormonal therapy prior to CDK4/6 inhibitor. CDK4/6 inhibitor was the first line in metastasis for 43.5% of the population, whereas it was not the first line for 56.5% of them. Letrozole was the most common combination in the first line treatment along with either palbociclib or ribociclib accounting for 56.5% among the patients, followed by fluvestant which accounted for 39.8% of the

combinations among the population. The median number of cycles completed by patients on the CDK4/6 inhibiting agent was 8 cycles. The detailed baseline characteristics are further illustrated in Table 9.

Table 9. Baseline characteristics of patients receiving CDK4/6 inhibitors

	All Population (N=108)	**Palbociclib Group (N=81)**	**Ribociclib Group (N=27)**
Age, mean (SD)	55.9 (10.6)	57.5 (10.5)	51.1 (9.5)
Nationality, n (%)			
Qatari	34 (31.5)	28 (34.6)	6 (22.2)
Egyptian	10 (9.3)	7 (8.6)	3 (11.1)
Sudanese	9 (8.3)	7 (8.6)	2 (7.4)
Syrian	8 (7.4)	3 (3.7)	5 (18.5)
Jordanian	5 (4.6)	4 (4.9)	1 (3.7)
Other Arab nationals	14 (13.0)	13 (16.1)	1 (3.7)
European	11 (10.2)	9 (11.1)	2 (7.4)
Philippino	8 (7.4)	5 (6.2)	3 (11.1)
Indian	4 (3.7)	3 (3.7)	1 (3.7)
Bengali	1 (0.9)	0 (0.0)	1 (3.7)
South African	2 (1.8)	1 (1.2)	1 (3.7)
Latin America nationals	2 (1.8)	1 (1.2)	1 (3.7)
Measurements, median (IQR)			
Hight (cm)	156.70 (8.00)	156.50 (8.65)	158.00 (11.80)
Weight (Kg)	74.70 (19.45)	75.00 (20.60)	74.00 (17.20)
BMI (Kg/m^2)	29.46 (8.14)	29.92 (8.55)	28.77 (6.05)
BSA (m^2)	1.81 (0.25)	1.81 (0.27)	1.81 (0.25)
Menopause Status, n (%)			
Pre-menopause	14 (13.0)	0 (0.0)	14 (51.9)
Perimenopause	5 (4.6)	0 (0.0)	5 (18.5)
Post-menopause	89 (82.4)	81 (100)	8 (29.6)
Breast Cancer Molecular Type, n (%)			
ER+ PR+ HER-2 –	84 (77.8)	62 (76.2)	22 (81.5)
ER+ PR – HER-2 –	24 (22.2)	19 (23.5)	5 (18.5)

	All Population (N=108)	Palbociclib Group (N=81)	Ribociclib Group (N=27)
Metastatic Diagnosis, n (%)			
De novo	39 (36.1)	28 (34.6)	11 (40.7)
Progressive	69 (63.9)	53 (65.4)	16 (59.3)
Metastasis Site, n (%)			
Lymph nodes only	17 (15.7)	13 (16.0)	4 (14.8)
Bones ± lymph nodes	42 (38.9)	32 (39.5)	10 (37.0)
Lungs with no liver	10 (9.3)	6 (7.4)	4 (14.8)
Liver	14 (13.0)	10 (12.3)	4 (14.8)
Other viscera	5 (4.6)	5 (6.2)	0 (0.0)
Bones and viscera	20 (18.5)	15 (18.5)	5 (18.5)
Receiving Prior HRT, n (%)			
Yes	87 (80.6)	67 (82.7)	20 (74.1)
No	21 (19.4)	14 (17.3)	7 (25.9)
Settings of Prior HRT, n (%)			
Adjuvant	60 (55.6)	45 (55.6)	15 (55.6)
Recurrent on HRT	29 (26.9)	18 (40)	11 (40.7)
Recurrence <1 year after completion HRT	9 (8.3)	7 (15.5)	2 (7.4)
Recurrence >1 year after completion of HRT	21 (19.4)	19 (42.2)	2 (7.4)
Metastatic	28 (25.9)	22 (27.2)	6 (22.2)
Received 1 line HRT prior to CDK4/6 inhibitor	17 (15.7)	15 (18.5)	2 (7.4)
Received 2 lines HRT prior to CDK4/6 inhibitor	9 (8.3)	5 (6.2)	4 (14.8)
Received >2 lines HRT prior to CDK4/6 inhibitor	2 (1.8)	2 (2.4)	0 (0.0)
CDK4/6 Inhibitor was the first line, n (%)			
Yes	47 (43.5)	33 (40.7)	14 (51.9)
No	61 (56.5)	48 (59.3)	13 (48.1)
CDK 4/6 Inhibitor Combination, n (%)			
AI (Anstrazole)	1 (0.9)	1 (1.2)	0 (0.0)
AI (Letrozole)	56 (51.9)	40 (49.4)	16 (59.3)
Fluvestrant	43 (39.8)	34 (42.0)	9 (33.3)
Shifting between AI and Fluvestrant	7 (6.5)	6 (7.4)	1 (3.7)
Tamoxifen	1 (0.9)	0 (0.0)	1 (3.7)
Number of CDK4/6 Inhibitor Cycles Completed, median (IQR)	8 (8)	9 (9)	6 (4)

A survival analysis using Kaplan Meier estimator was used in order to

investigate the progression free survival (PFS) and the overall survival (OS) associated with both palbociclib and ribociclib was all possible indicated combination. As for the PFS, the mean (standard error) PFS time for the palbociclib group in months was 17.85 (1.40) 95% confidence interval (CI) [15.11 – 20.59], whereas it was 13.55 (1.66) with a 95% CI of [10.29 – 16.80] for the ribociclib group. The difference of the two groups in terms of PFS was not statistically significant based on the log-rank's test score (p=0.28), and Breslow test (p=0.265). Around 50% of the patients had progression free for 14 months in the palbociclib treatment group, whereas around 50% of the patients had progression free disease for 11 months in the ribociclib group. The detailed progression free survival functions in relation to time are indicated in Table 10, and the PFS survival curve is illustrated in Figure 4.

Table 10. Kaplan-Meier's survival table of the progression-free survival for palbociclib and ribociclib

Time in Months	**Survival Function**	**Number of Patients Remaining**
Palbocicilb (n=81)		
3	0.975	79
4	0.962	70
5	0.934	68
6	0.906	65
7	0.862	58
8	0.816	54
9	0.771	51
10	0.722	44
11	0.687	39
12	0.572	30
13	0.553	29
14	0.533	27
15	0.474	24
16	0.392	19
17	0.370	17
20	0.343	13
22	0.264	10

Time in Months	Survival Function	Number of Patients Remaining
23	0.238	9
30	0.198	5
33	0.159	4
34	0.106	2
Ribociclib (n=27)		
4	0.880	22
5	0.838	20
7	0.792	17
9	0.643	13
11	0.526	9
13	0.438	5
14	0.329	3
20	0.219	2
23	0.000	0

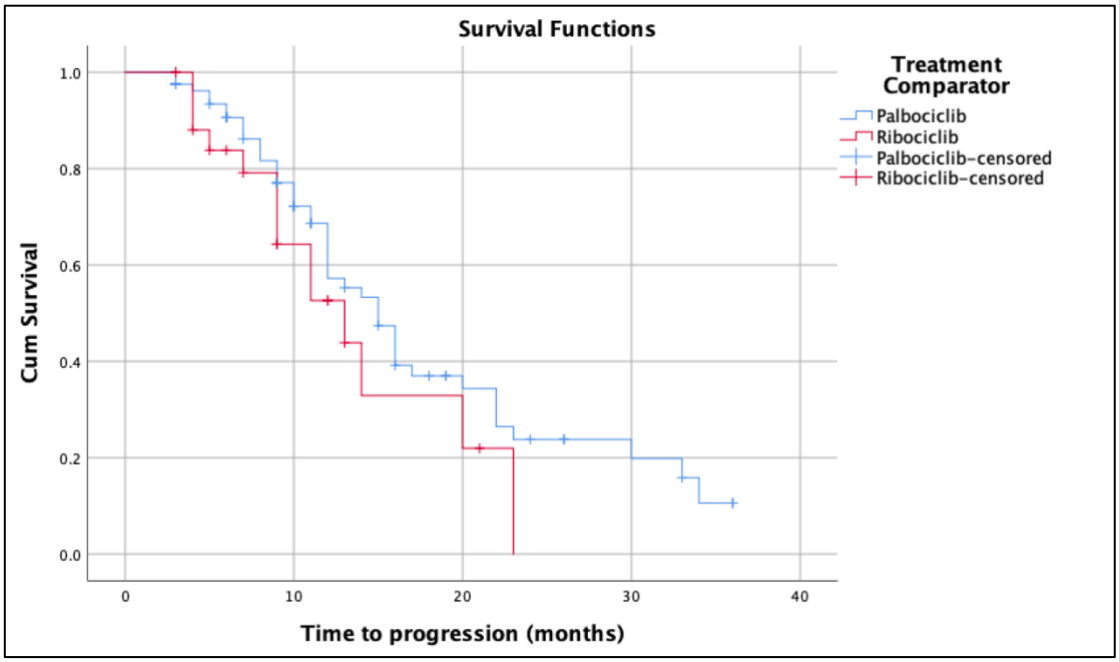

Figure 4. Kaplan-Meier's survival curves of the progression-free survival for palbociclib and ribociclib

On the other hand, as for the overall survival (OS) of palbociclib and ribociclib, the time until death during the study period was estimated using Kaplan Meier analysis.

The mean (standard error) OS time for the palbociclib group in months was 29.82 (1.31) with a 95% CI of [27.26 – 32.39], whereas it was 31.72 (3.65) with a 95% CI of [24.57 – 38.87] for the ribociclib group. The difference of the two groups in terms of PFS was neither statistically based on the log-ranks test (p= 0.982), and nor on the Breslow test (p=0.665). The OS survival functions in relation to time are indicated in Table 11, and the OS survival curve is illustrated in Figure 5.

Table 11. Kaplan-Meier's survival table of the overall survival for palbociclib and ribociclib

Time in Months	**Survival Function**	**Number of Patients Remaining**
Palbocicilb (n=81)		
5	0.986	72
9	0.956	63
10	0.940	59
11	0.924	56
12	0.906	52
13	0.889	51
14	0.870	47
16	0.850	43
18	0.829	39
23	0.801	28
25	0.728	20
26	0.687	17
28	0.642	14
33	0.588	11
Ribociclib (n=27)		
6	0.958	23
22	0.799	5
36	0.000	0

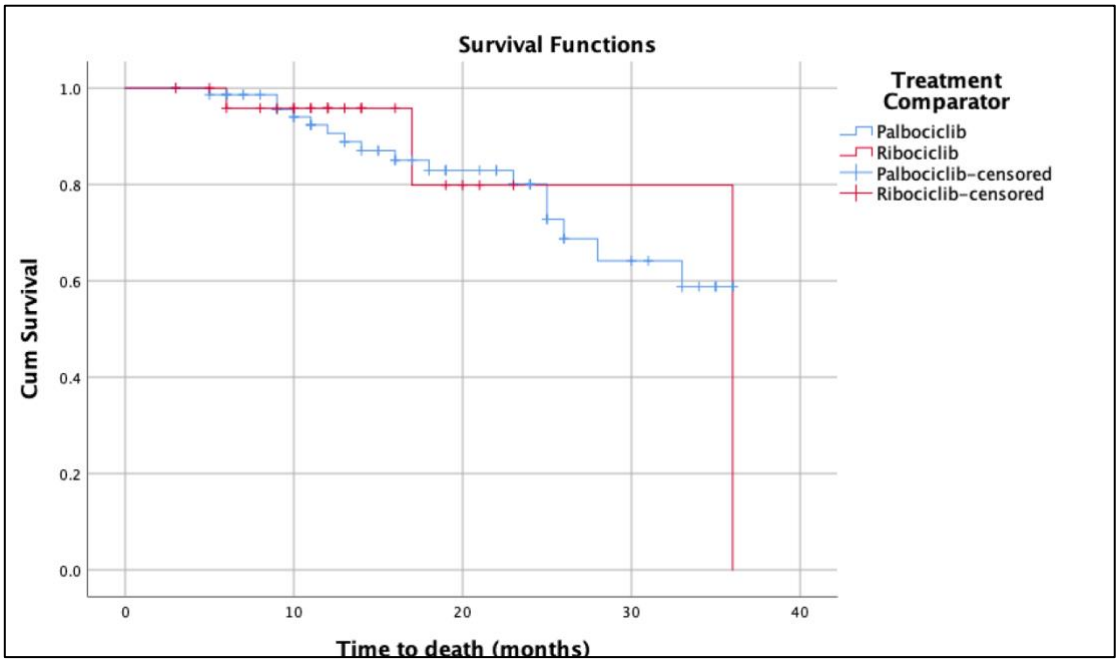

Figure 5. Kaplan-Meier's survival curves of the overall survival for palbociclib and ribociclib

In order to investigate the effect of the baseline characteristics on the survival functions of the PFS and OS, a COX regression was conducted. The results of the cox-regression analysis showed that none of the baseline covariates that were analyzed in the model was significantly associated with a change in neither the PFS nor in the OS. That is, for the progression free survival, the overall value of chi-square test for the model was 5.531 (p=0.938). As for the detailed covariates, none of them was statistically significant contributor to the PFS 'age' (p=0.644), 'menopausal status' (p=0.748), 'the diagnosis of metastasis' (p=0.246), 'the type of the metastasis' (p=0.902), 'the receiving of prior hormonal therapy' (p=0.472), 'the CDK4/6 agent' (p=0.231), and 'the CDK4/6 combination medication' (p=0.548). Similarly, for the overall survival, the overall chi-square test for the model did not show significance (7.389, p= 0.831). As for the detailed covariates, none of them reached significance level; 'age' (p=0.725), 'menopausal status' (p=0.756), 'the diagnosis of metastasis'

(p=0.071), ‘the type of the metastasis’ (p=0.699), ‘the receiving of prior hormonal therapy’ (p=0.990), ‘the CDK4/6 agent’ (p=0.591), and ‘the CDK4/6 combination medication’ (p=0.608).

Of note, 42 patients have not stopped their medication until the end of the study observational period; 33 patients in the palbociclib group, and nine patients in the ribociclib group. For those 66 patients who stopped their CDK4/6 inhibitor medications, 74.2 % of them stopped it due to disease progression (n=49), 13.6 % due to side effects (n=9), 1.5 % due to death (n=1), 3% due to other reasons such as financially being unable to cover the treatment expenses and undergoing a near surgery that required the stop of medication (n=2), and 7.6% were lost to follow up (n=5). Out of those patients who developed progression throughout the study period (n=56), 10.7% had progression only in lymph nodes (n=6), 21.4% had it in bones ± lymph nodes (n=12), 28.6% had it in liver (n=16), 8.9% had it in other organs such as adrenal cortex and brain (n=5), 30.4% had their progression in both bones and viscera (n=17).

Regarding the safety outcomes (ADRs outcomes), blood-related side effects and toxicities were the most common among all patients accounting for 73.1% of all the population (n=79). Neutropenia was the most common (n=64), followed by thrombocytopenia (n=5), anemia (n=4), febrile neutropenia- i.e.: neutropenia with a fever (n=3), pancytopenia (n=3), and lastly leukopenia (n=1). The blood-related side effects were mostly of a mild to moderate intensity where grade 1 was present in 49.4% of the patients who developed blood-related side effects (n=39), and grade 2 was present in 34.2% (n=27). As for grade 3 blood-related toxicities, they were present in 13.9% of the patients, and grade 4 were present in only 1.3% of the patients (n=1). As for the grade 1 blood-related side effects, they were mostly associated with no clinical management or with only monitoring (n=12). Whereas, grade 2 and 3 blood-related

side effects were associated with withholding treatment followed by dose reduction (n=25), or with only postponing the treatment and restarting at the same dose if a patient had only grade 2 side effects but stable (n=13). For grade 4 side effects, the CDK4/6 inhibitor drug was stopped immediately (n=1). Hospitalization due to blood-related side effects were not included at the clinical management for grade 4 side effects except for 5% of the patients (n=4): three due to febrile neutropenia, and one due to grade 3 anemia that was also associated with lower functionality and need for blood transfusion. Concerning the gastric side effects, only 7.4% patients of the total population experienced gastric side effects because of CDK4/6 inhibitors (n=8). Out of those who experienced gastric side effects, diarrhea ± abdominal pain was the most common among them and was only managed with only diarrhea medications such as oral loperamide (n=5). Nausea and vomiting were present only in two patients, and had no significant clinical management, whereas constipation was present in only one patient and was managed with constipation treatment therapy (lactulose). For the cardiac side effects, QT interval prolongation occurred in 5.6% of the patients (n=6) with an average value of 493 ± 25. It was managed by delaying the treatment until the normalization of the QT value in all the cases. Another rare cardiac side effect that occurred only in one patient and leaded to patient death was CDK4/6 inhibitor induced atrial fibrillation. Unfortunately, this side effect was detected after the patient death, and therefore, it was associated with only the same clinical management of the traditional atrial fibrillation. Hepatotoxicity due to CDK4/6 inhibitors occurred in only 1 patient (0.9% of the total population) where the liver enzymes Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated with values of 255 u/L and 85 u/L respectively. This liver toxicity was managed with a dose reduction of the CDK4/6 inhibitor (palbociclib). Lastly, for other side effects, 4.6% of the population developed fatigue

(n=5) that was mostly managed with only monitoring and follow up with patients, but only one patient had to stop her CDK4/6 inhibitor since her fatigue affected her performance status to be of an ECOG PS 3. Peripheral neuropathy with associated symptoms of numbness and tingling was present in 2.8% of the population and was managed by referrals to neurologist in all cases. Skin rashes of grade 1 and 2 also occurred in 2.8% of the population and was managed by systematic antihistamines ± topical medications. Lastly, dry eyes syndrome occurred in 1.9% of the population (n=2) and was managed topical eyes lubricants regularly. The side effects in all the population, and in specific to palbociclib and ribociclib are summarized in Table 12.

Table 12. Safety outcomes for the study population (ADRs)

Side Effect	**All Patients (N=108)**	**Palbococlib Group (N=81)**	**Ribociclib Group (N=27)**
Blood- Related Side Effects, n (%)	64 (59.3)	46 (56.8)	18 (66.7)
Neutropenia	3 (2.8)	3 (3.7)	0 (0.0)
Febrile Neutropenia	1 (0.9)	1 (1.2)	0 (0.0)
Leukopenia	5 (4.6)	3 (3.7)	2 (7.4)
Thrombocytopenia	3 (2.8)	3 (3.7)	0 (0.0)
Anemia	3 (2.8)	3 (3.7)	0 (0.0)
Pancytopenia			
Cardiac Side Effects, n (%)			
QT-Interval Prolongation	6 (5.5)	1 (1.2)	5 (4.6)
Induced Atrial Fibrillation	1 (0.9)	1 (1.2)	0 (0.0)
GI Side effects, n (%)			
Diarrhea	5 (4.6)	4 (4.9)	1 (3.7)
Constipation	1 (0.9)	1 (1.2)	0 (0.0)
Nausea and Vomiting	2 (1.8)	2 (2.4)	0 (0.0)
Hepatotoxicity, n (%)	1 (0.9)	1 (1.2)	0 (0.0)
ALT and AST level, (u/L)	255, 85	255, 85	-
Other Side Effects, n (%)			
Fatigue	5 (4.6)	4 (4.9)	1 (3.7)
Peripheral Neuropathy	3 (2.8)	2 (2.4)	1 (3.7)
Skin Rash	3 (2.8)	2 (2.4)	1 (3.7)
Dry Eyes Syndrome	2 (1.9)	2 (2.4)	0 (0.0)

4.2. Results of Phase 2: Pharmacoeconomic Analysis

4.2.1. Results of cost analysis of CDK4/6 inhibitors.

Regarding the assumption of the non-normality of the overall cost data, the Kolmogorov-Smirnov test confirmed this assumption ($p < 0.001$), hence, non-parametric statistics were executed. Both direct medical costs of the PFS and progressed disease (PD) status were calculated arithmetically for the actual patient data obtained from phase I. Regarding the PFS cost, overall, there was no statistically significant difference between the point estimates for the two treatment groups. The median direct medical cost (IQR) of palbociclib per patient per month was of QAR 11,628.5 (QAR 7477.41– QAR 14316.4), whereas it was of QAR 10,285.09 (QAR 8926.43– QAR 11,054.17); $p=0.064$. Due to confidentiality issues and the signed data no-share agreement by HMC, the detailed unit costs cannot be summarized in this report. However, the median total unit consumption costs per patient per course of treatment and the total estimated cost per course of treatment summarized in Table 13.

As for the factors influencing the overall drug cost, the results of the GLM revealed that both age and recipient of prior hormonal therapy were of a significant effect on the overall costs with B-intercepts of 0.705 [95% CI (0.304 – 1.106)]; ($p= 0.001$), and 0.022 [95% CI (0.006 – 0.037)]; ($p= 0.005$) respectively. However, for other factors included in the model did not reach the level of significance with p-values for menopausal status ($p=0.426$), molecular subtype ($p=0.165$), metastasis diagnosis ($p=0.221$), and metastasis type ($p=0.850$). In terms of the goodness of fit, the overall GLM model had an under-dispersion with a value/degree of freedom of 0.61. Nonetheless, based on the omnibus test, it was significant with a p-value of 0.005. Based on the results of the GLM, the total additional total direct medical cost for the PFS status for both palbociclib and ribociclib can be explained according to the listed Equation 6 below.

Total Direct Medical Costs = 0.705 (Recipient of a prior HRT) + 0.022 (Age) + 9.123

Equation 6. Additional total direct medical costs explained by baseline characteristics. The recipient of a prior hormonal therapy is given a value of 1 if a patient has received a prior hormonal therapy, and a value=0 if a patient has not. Age is in years.

According to the clinician collaborators from the NCCCR and the published international guidelines, the management of the progression does not differ based on the recipient of a specific CDK4/6 inhibiting agent. Therefore, overall PD cost was calculated for both treatment arms together and assumed to be the same. The median (IQR) PD cost per patient per month was QAR 2,224.34 (QAR 1,893.9 – QAR 4,118.3). The cost analysis of PD was based on the following costs: first line and second line treatments of chemotherapy and hormonal therapy drug acquisition costs, lab tests cost, clinical imaging and radiology cost, cardiac procedure cost, hospital visits and administration costs. Same to PFS cost analysis, due to the confidentiality agreement, the detailed unit costs cannot be summarized in this report. However, the median (IQR) total unit consumption costs per patient per course of treatment and the total estimated direct medical cost per course of treatment summarized in Table 14.

Table 13. Cost analysis of the direct medical components of palbociclib and ribociclib treatments in the PFS status

	Cost Driving Unit	Total Population N= 108	Palbociclb N=81	Ribociclib N=27
Total Unit Consumption Cost in Qatari Riyals (QAR), Median (IQR)	*Total Drug acquisition cost*	153,923 (152,149)	185,023 (169,951)	110,728 (78,238)
	Palbociclib 125 mg	113,886 (154,558)	113,886 (154,558)	N/A
	Palbociclib 100 mg	82,481 (98,978)	82,481 (98,978)	N/A
	Palbociclib 75 mg	53,171 (106,343)	53,171 (106,343)	N/A
	Ribociclib 600 mg	106,214 (70,810)	N/A	106,214 (70,810)
	Ribociclib 400 mg	11,802 (11,802)	N/A	11,802 (11,802)
	Ribociclib 200 mg	-	N/A	-
	Anstrazole 1 mg	3,452 (0)	3,452 (0)	-
	Letrozole 2.5 mg	4,078 (3,568)	4,587 (4,587)	3,568 (2,039)
	Fluvestrant 500 mg	31,103 (35,547)	39,990 (33,325)	17,773 (7,776)
	Tamoxifen 10 mg	1,350 (0)	-	1,350 (0)
	Total Lab Tests	9,145 (9,273)	9,770 (9,825)	8,620 (8,220)
	CBC	420 (440)	480 (480)	360 (160)
	Blood Chemistry	900 (900)	1,080 (945)	810 (473)
	Endocrinology	660 (1100)	770 (935)	660 (715)
	Tumor markers and CA	6,750 (6750)	7,875 (7,313)	6,750 (5,500)
	Coagulation	140 (245)	140 (210)	140 (210)
	Urine Analysis	60 (90)	60 (105)	60 (0)
	Total Clinical Imaging	7,080 (9,362)	7,080 (9,390)	9,620 (9,430)
	X-ray	100 (100)	100 (112)	50 (37.5)
	Ultrasound	220 (220)	220 (220)	220 (220)
	CT Scan	490 (489)	490 (490)	980 (490)
	MRI	3,120 (3,120)	3,120 (3,120)	1,560 (5,460)
	PET Scan	9,620 (9,620)	9,620 (9,620)	9,620 (9,620)
	Mammogram	340 (0)	340 (0)	340 (0)
	DEXA	4,350 (0)	4,350 (0)	4,350 (0)

	Cost Driving Unit	Total Population N= 108	Palbociclb N=81	Ribociclib N=27
	Total Cardiac Procedure	120 (122)	110 (150)	120 (98)
	ECG	80 (80)	40 (40)	120 (89)
	ECHO	110 (110)	110 (55)	110 (110)
	Total Hospital Costs	525 (600)	600 (600)	350 (450)
	Outpatient visits	350 (438)	400 (450)	250 (300)
	Inpatient hospitalization	300 (600)	250 (775)	400 (600)
	Total Direct Medical Cost	172,534 (162,706)	207,569 (181,790)	139,363 (162,706)

Table 14. Cost analysis of the direct medical components of the PD status

	Cost Driving Unit	Per Progressed Patients N= 49	Unit	Per Progressed Patients N= 49
Total Unit Consumption Cost in Qatari Riyals	*Total Chemotherapy Acquisition Cost*	15,171 (15,023) 15,170 (16,434)	*Total Hormonal Therapy Acquisition Cost*	30,983 (28,244) 33,920 (49,221)
	Capcitabine (n= 32)	8,611 (10,663)	Exemestane/ Everlimus (n= 18)	17,773 (13,329)
	CMF/ DC (n=17)	9,382 (11,727)	Fluvestrant (n= 11)	
	Eribulin (n=5)			
	Total Lab Tests	4,780 (9,155)	*Total Clinical Imaging*	6,860 (10,055)
	CBC	400 (320)	X-ray	100 (160)
	Blood Chemistry	1,560 (1,820)	Ultrasound	50 (100)
	Endocrinology	80 (160)	CT Scan	490 (0)
	Tumor markers and CA	6,750 (11,250)	MRI	3,120 (4,680)
			PET Scan	9,260 (9,260)

	Cost Driving Unit	Per Progressed Patients N= 49	Unit	Per Progressed Patients N= 49
	Total Cardiac Procedure	110 (155)	*Total Hospital Costs*	650 (1,375)
	ECG	80 (120)	Outpatient visits	300 (250)
	ECHO	110 (110)	Inpatient hospitalization	1,150 (1,825)
	Total Direct Medical Cost	29,426 (50,412)		

4.2.2. Results of the cost-effectiveness and cost-utility analysis of CDK4/6 inhibitors.

In correspondence of the primary outcome of the study, the cost-effectiveness and the cost-utility of the two treatment strategies, a 10-year within-cycle corrected Markov's model was performed. The long-term Markov's model analysis showed that overall ribociclib treatment arm was slightly dominant over palbociclib. That is, the 10-year cost of the palbociclib treatment strategy was 372,663.3 QAR. In accordance, it has yielded a gain of 5.968 life years (LYs) and overall gained quality adjusted life month of 36.7 months (3.058 QALYs). Whereas, for ribociclib treatment arm, the overall 10-year cost was 333,584.4 QAR. Similarly, it has yielded 6.330 gained life years 3.160 QALYs. Comparing each of the two-treatment arms cost/QALYs to the recommended WTP threshold of cost effectiveness, 576,150 QAR, both medications yielded an overall cost less than the WTP threshold. In addition, both of them are considered very cost-effective when compared to the 1 GDP threshold, 192,050 QAR per QALY- 121,865 QAR/QALY for palbociclib and 105,564.7 QAR/QALY for ribociclib. The costs and effectiveness values were incremented to compare the two treatment options using the previously illustrated Equation 1. It was shown that the ICUR was -31,868.06 QAR per every gained QALY for the use of ribociclib over palbociclib, suggesting that ribociclib is more cost-saving and more effective option. Assuming the same WTP threshold for life years gained as well, ribociclib was a more cost-effective option than ribociclib with an ICER of − 83,090.88 QAR/ LY (less than the 3 GDP and 1 GDP WTP threshold). Therefore, ribociclib is considered a very cost-effective option compared to palbociclib as can be shown in Figure 6. Also, the detailed values for cost and effectiveness are shown in Table 15.

Table 15. Base-case results for palbociclib and ribociclib treatment groups

	Palbociclib	**Ribociclib**	**Palbociclib minus Ribociclib**
Cost (QAR)			
Total Cost	372,663.3	333,584.4	39,078.9
PFS Cost	229,563.45	154,170.39	75,393.06
PD Cost	143,099.89	179,414.02	− 36,314.13
Effectiveness Outcomes			
Life Years Gained	5.968	6.330	− 0.362
QALYs Gained	3.058	3.160	− 0.102
Incremental Ratios			
ICER	-	-	− 83,090.88
ICUR	-	-	− 31,868.06

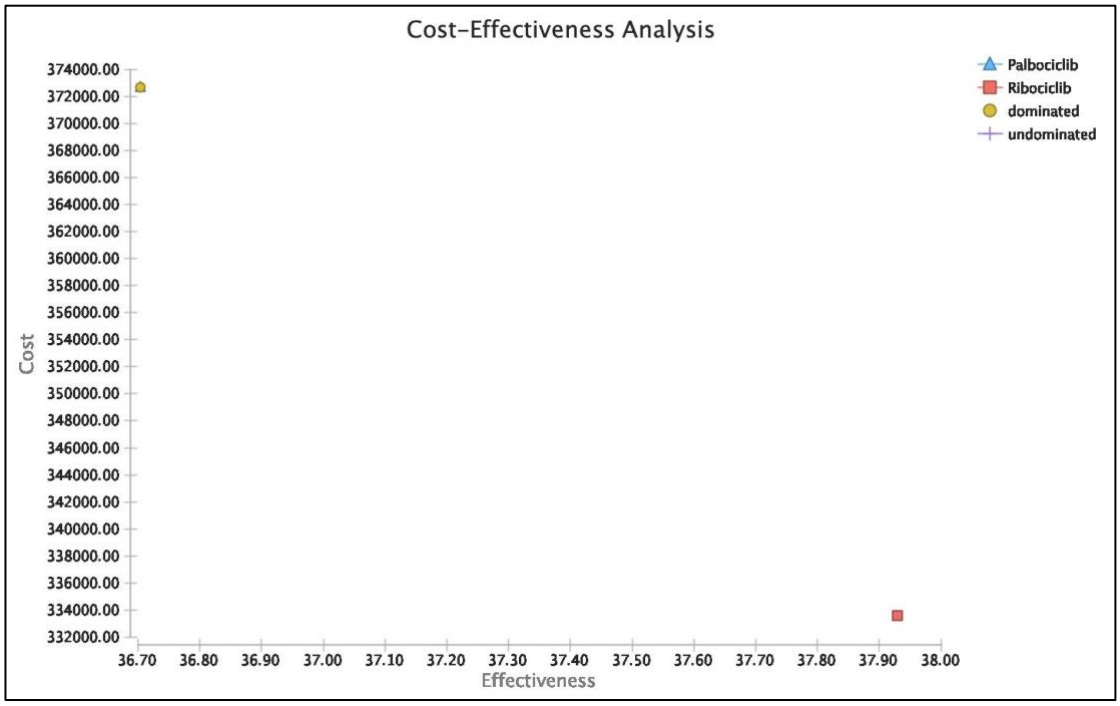

Figure 6. Cost-effectiveness analysis graph of palbociclib and ribociclib. Effectiveness values are expressed in quality adjusted life months. Cost values are expressed in Qatari Riyals.

Regarding the univariate deterministic sensitivity analysis, sates costs, transition probabilities, and utilities were varied as explained earlier in Chapter 3. The cost of PFS in the palbociclib was the first parameter that was tested by the sensitivity analysis. The conclusion of the favoring ribociclib as a more cost-effective and cost-useful analysis remained robust against the variation of the cost of PFS for the palbociclib group. However, it was shown that palbociclib was not dominated as described previously at a cost of PFS that equals 9,612.9 QAR (17.33% reduction of the input cost); however, it was still less cost-effective than ribociclib in total (ICUR = 5572.79 QAR/QALY gained per patient). Similarly, in absence of any other uncertainties, the conclusion of the cost-effectiveness and cost-utility of the two medications remained the same keeping ribociclib a more dominant option over palbociclib with +/- 20% adjustment in the total cost of PFS cost of ribociclib; ICUR ranged from -6,723.5 QAR/QALY to -57,012.6 QAR/QALY. As for the transition probabilities of PFS to PD in the palbociclib arm, when applying the uncertainty range of (0.0459 – 0.05035), the conclusion of having ribociclib dominant over palbociclib remained robust against this uncertainty variation in absence of any other uncertainties; ICURs ranged from -10,685.9 QAR/QALY to -31,868.1 QAR/QALY. On the other hand, for the monthly probability of PFS to PD for the ribociclib group, ribociclib remained more cost-effective than palbociclib when the probability was varied according to the MONALEESA-2 trial; nonetheless it was dominant only when the probability is more than or equals 0.04537 (25% variation from the base-case probability). The uncertainty regarding the probability of PFS to PD in the ribociclib treatment arm was associated with an ICUR ranging from 12,894.35 QAR/QALY to -31,868.06 QAR/QALY. Lastly, the utility associated with the PFS of palbociclib was varied according to the 95% CI range of the case-base (0.7387 – 0.7627). The

conclusion of the cost-effectiveness of ribociclib over palbociclib remained robust over that range of uncertainty where ribociclib was dominant over palbociclib over all the uncertainty range; ICUR (-26,458.52 QAR/QALY to -39,498.59 QAR/QALY). Similarly, the conclusion of the cost-effectiveness of ribociclib over palbociclib remained robust when the utility of PFS in the ribociclib group was varied by 18.5% according to the standard deviation associated with the utility value as obtained from literature. That is, ribociclib was more cost-effective than palbociclib all over the uncertainty range, however, it did not dominate at utility values less than 0.622; ICUR ranged from 54,664.07 QAR/QALY to 198,120.36 QAR/QALY. Lastly, the utility of progressed disease was varied at +/- 20%, and the conclusion of the domination of ribociclib over palbociclib remained robust all over the range; ICER ranged from -338,058.56 QAR/QALY to -16,722.21 QAR/QALY.

A tornado diagram was implemented to show the impact of each of the sensitivity analysis factors on the overall cost-effectiveness of the two strategies. As illustrated in figure. 6, the inputs that affected ICUR are arranged based on their impact from the top to the bottom. The blue color indicates the parameter, and the red color indicated the ICER. As can be shown in the figure, the uncertainty of the utility of the progressed disease (U_PD) had the highest impact on the ICER; as it goed up, the ICER increased. This was followed by the uncertainty regarding costs of the PFS health states in the palbociclib (C_PFS_Palbo) and ribociclib (C_PFS_Ribo) treatments. The uncertainties regarding the transition probabilities of PFS to PD in both ribociclib (P_PFS_Ribo) and palbociclib (P_PFS_Palbo) had a very limited effect on the ICER. That is, as per the diagram, the higher the P_PFS_Ribo changes, the very minor decrease in ICER occurs. Oppositely, with a minor change in the P_PFS_Ribo, ICER increases slightly. The utility of the PFS in the palbocilcib group

(U_PFS_Palbo) was showing to lower the ICER when it increases. The increase of the cost of the progression (C_PD) was shown to have a very limited effect on the ICER, whereas the uncertainty of the utility in PFS in the ribociclib group was associated with undefined effect on ICER. The uncertainty with all of the variables did not cross the WTP threshold for the cost effectiveness, suggesting that ribociclib remains a more cost-effective option than palbociclib in all cases. The whole sensitivity analyses parameters and their effects on the ICER are shown in figure 7. In addition, although the net monetary benefit was not of the outcomes of this research, the tornado diagram was plotted against the net monetary benefit for more clarification and illustration. The results are consistent with what was drawn by the tornado diagram on ICER as can be illustrated in the below figure 8. All the sensitivity analysis inputs, outputs, as well as the case base values are summarized in Table 16.

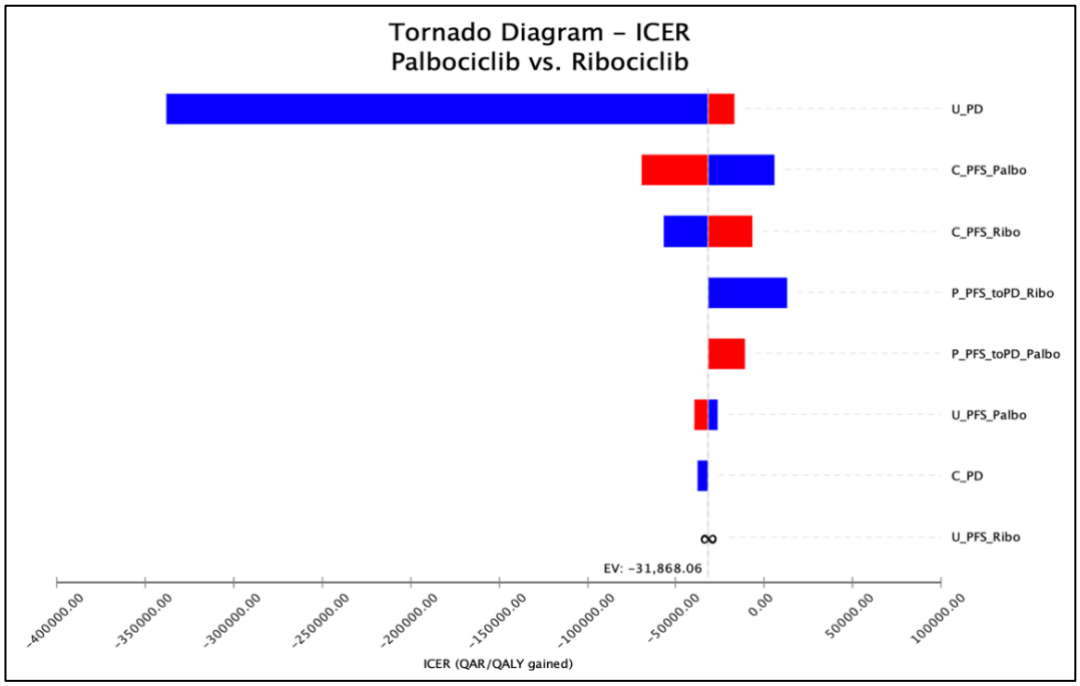

Figure 7. Tornado diagram of the univariate sensitivity analyses and their Impact on ICER. Blue color represents the parameter, whereas the red color represents the ICER. ICERs are ICURs (QAR/QALY).

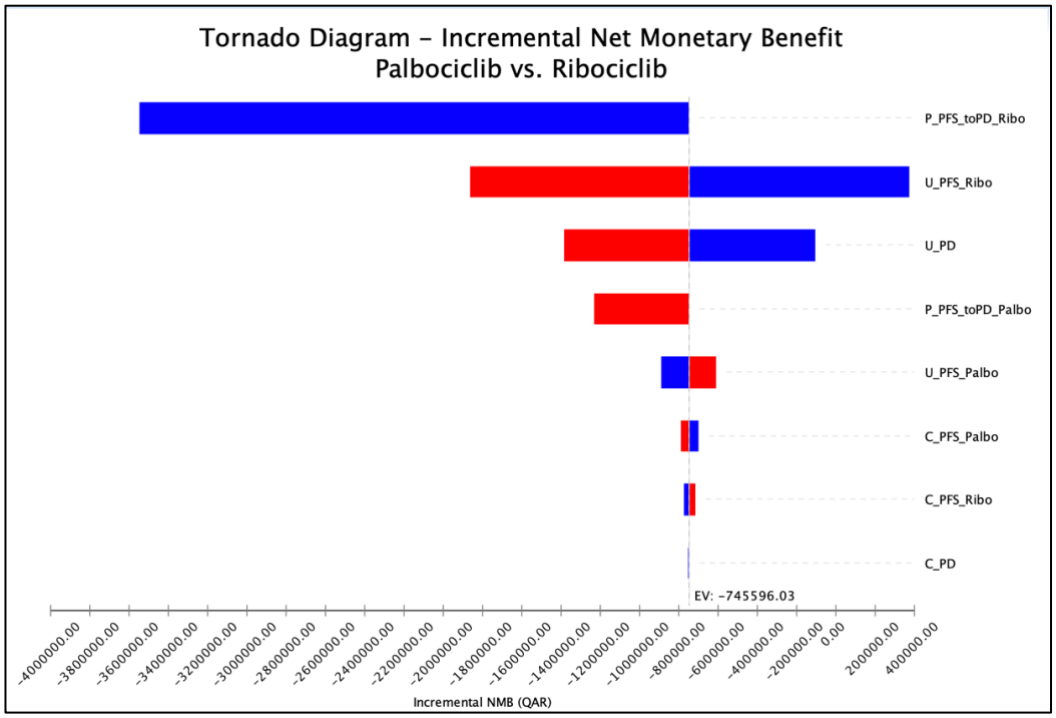

Figure 8. Tornado diagram of the univariate sensitivity analyses and their impact on incremental net monetary benefit (NMB). Blue color represents the parameter, whereas the red color represents the NMB. NMB are expressed in Qatari riyals.

Table 16. Univariate sensitivity analyses inputs and outputs

Input Parameter	**Base-case Value**	**Sensitivity analysis boundaries**		**ICER range (QAR/QALY)**	
		Lower boundary	Upper boundary	Lower boundary	Upper boundary
Cost of PFS State for Palbociclib (QAR)	11,628.5	9,302.8	13,954.2	-69,308.9	5,572.8
Cost of PFS State for Ribociclib (QAR)	10,285.1	8,228.1	12,342.1	-57,012.6	-6723.5
Cost of Progressed Disease state (QAR)	2,942.6	2,354.1	3,531.1	-37,790.7	-25,945.4
Monthly Probability for PFS to PD in Palbociclib	0.04597	0.04597	0.05036	-31,868.1	-10,685.9
Monthly Probability for PFS to PD in Ribociclib	0.05887	0.0261	0.05887	-31,868.1	12,894.4
Utility of PFS State for Palbociclib	0.7507	0.738	0.7627	-39,498.7	-26,458.5
Utility of PFS state for Ribociclib	0.7	0.5705	0.8295	-63,4670	198,120.3

Input Parameter	Base-case Value	Sensitivity analysis boundaries		ICER range (QAR/QALY)	
		Lower boundary	Upper boundary	Lower boundary	Upper boundary
Utility of Progressed Disease State	0.45	0.36	0.54	-33,8059	-16,722.2

As for the probabilistic sensitivity analysis, the Monte-Carlo simulation was conducted to generate 10,000 simulations. As per the generated 10,000 results, the mean (SD) lifetime cost of palbociclib was 386,778.1 (196,998.1) QAR with an average (SD) gained QALYs of 3.135 (0.8725) QALYs. For the ribociclib treatment group, the mean (SD) lifetime cost according to the generated simulatations was 354,057.03 (152,369) QAR with an average (SD) gained QALYs of 3.246 (1.0425) QALYs. Therefore, it suggests that both medications are cost-effective even when applying the Monte-Carlo simulation for the combined inputs uncertainties. The CE scatterplot, figure 9, confirms this conclusion by having the points representing the two treatment strategies plotted against the two axes of the cost and effectiveness. To graphically test the case-base conclusion of preferring ribociclib over palbociclib, the ICE of ribociclib versus palbociclib was generated (figure 10). According to the figure, the major distribution of the generated scenarios showed that ribociclib was more effective and less costly in 26.14%, whereas it was more costly but more effective (more cost-effective) in 32.87% of the cases. Nonetheless, it was less costly but less effective than in 24.65% of the cases, and inferior to palbociclib in 15.16% of the cases.

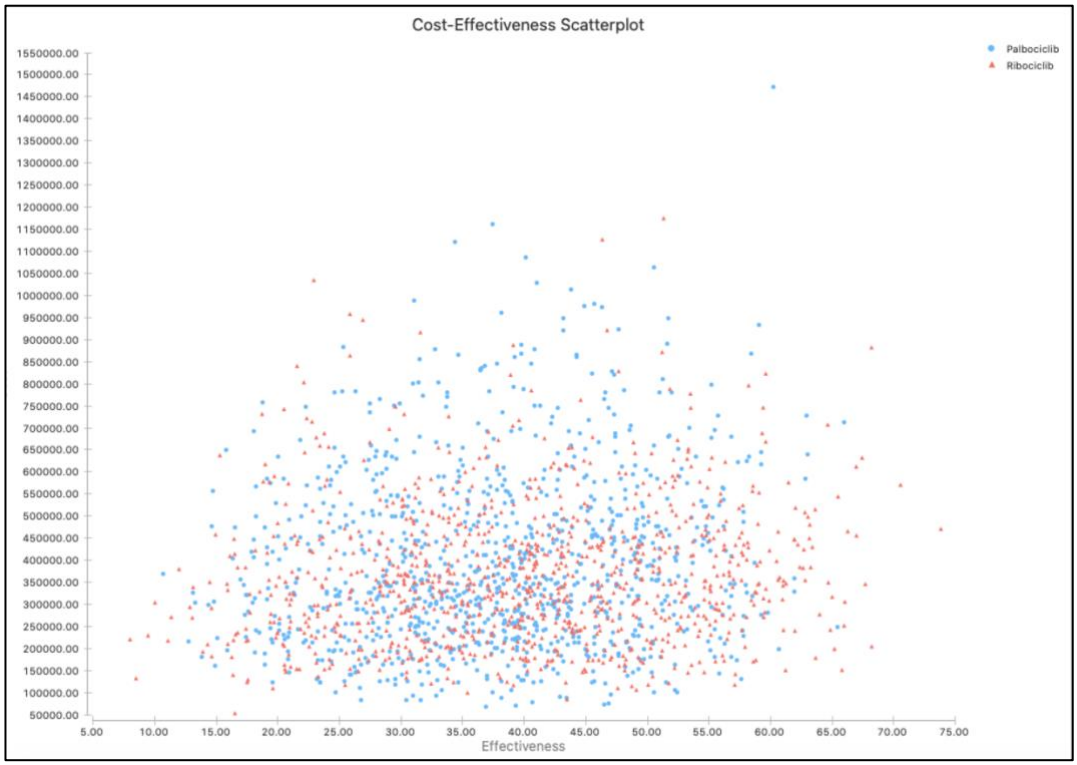

Figure 9. CE scatterplot of palbociclib and ribociclib treatment strategies by Monte-Carlo simulation for probabilistic sensitivity analysis. Dots are dispersed suggesting that both palbociclib and ribociclib have similar effectiveness and cost.

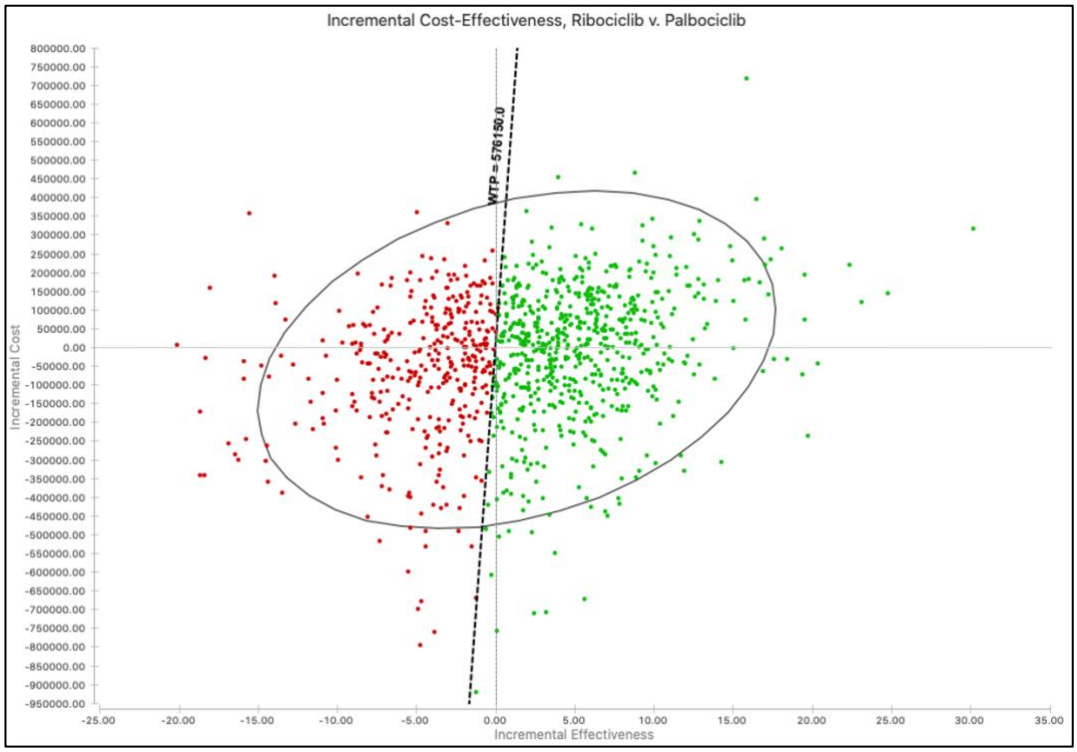

Figure 10. ICE plot of ribociclib versus palbociclib. Green dots are ribociclib scenarios and red dots represent the palbociclib. More than half of the hypothetical scenarios prefer ribociclib over palbociclib.

The Monte-Carlo acceptability at the current WTP threshold (576,150 QAR) was calculated. It was shown that ribociclib remained a more cost-effective option than palbociclib at 59.79% of the cases. In addition, it remained a more cost-effective option in 60.5% of the cases at the very cost-effectiveness WTP (192,050 QAR). Lastly, to investigate the impact of the change in the WTP on the cost-effectiveness conclusion of both treatment strategies, the CE acceptability curve was generated (figure 11). As can be seen in figure 10, both palbociclib and ribociclib remained cost-effective options with the increase in the WTP threshold; ribociclib was a more cost-effective option compared to palbociclib overall (51.57% of the results preferred ribociclib over palbociclib).

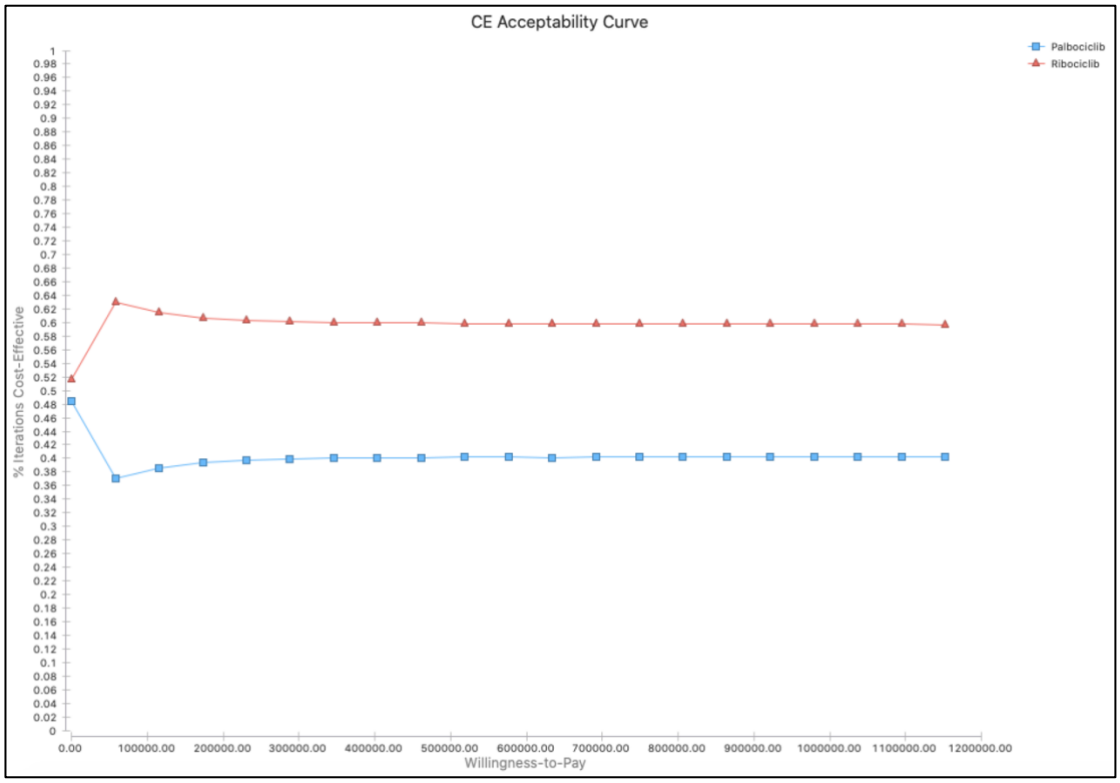

Figure 11. Cost-effectiveness acceptability curve at different WTP threshold values. Both palbociclib and ribociclib remain cost-effective options with the increase in WTP threshold with more favorable results for ribociclib over palbociclib.

Chapter 5: Discussion

The present study was carried out in two phases with the purpose of evaluating the clinical effectiveness, cost-effectiveness and cost-utility of two CDK4/6 inhibitors, palbociclib and ribociclib. Consequently, the study findings will be discussed below in the same sequence of the two phases.

5.1. Discussion of Phase 1: Clinical Phase

CDK4/6 inhibitors are now included in the first-line treatment of HR+/HER-2 advanced breast cancer in addition to endocrine therapy. This phase of the project is considered the first retrospective observational study evaluating and comparing the efficacy of two of the CDK4/6 inhibiting medications used in the first-line treatment of HR+/HER2- stage IV breast cancer patients, with an evaluation for their safety profiles as well. It aimed to evaluate the overall efficacy of the two used CDK4/6 inhibitors, palbociclib and ribociclib, by determining and comparing their both PFS and OS. In addition, it aimed to give an insight about the safety profiles of both medications. With regards to the efficacy, overall, there was no statistically significant difference in the efficacy endpoints between the two comparators, palbociclib and ribociclib, with their treatment combinations. That is, in terms of the PFS of the two treatment strategies, the mean PFS in the palbociclib treatment group was of 17.85 months, whereas it was 13.55 months in the ribociclib group; nonetheless, the p-value was 0.2 which did not reach the level of significance. Similarly, for the overall survival, the mean survival time for the palbociclib group was 29.82 months and for the ribociclib it was 31.72, but also without reaching to the significance level. Additionally, in regard to the safety profiles, the most common blood-related side effects, cardiac toxicities, gastro-intestine (GI) side effects, and hepatotoxicity were

evaluated in the two treatment arms, and the ratio was found to be equivalent between both. Therefore, the present results would indicate that both medications are equivalent in terms of their efficacy and safety to much extent.

To date, there is no head-to-head randomized controlled trials (RCTs) comparing palbociclib and ribociclib in the treatment of stage IV HR+/HER-2 negative breast cancer population. Nonetheless, overall, the findings of our study were consistent to much extent with the large population published phase III trials. That is, in an adjusted indirect analysis of the phase III RCTs of CDK4/6 inhibitors, there was no statistically significant difference between palbociclib with its indicated combinations and ribociclib and its indicated combinations in terms of PFS as an indicator of effectiveness. The overall relative risk for palbociclib versus ribociclib according to this analysis in terms of PFS was 0.91 [95% CI (0.75- 1.11)], suggesting that there is no difference between the two treatment strategies (138). In our study, there was also no statistically significant difference between palbociclib and ribociclib with their indicated combinations in the treatment of stage IV HR+/HER-2 negative breast cancer patients; 17.85 months [95% CI (15.11 – 20.59)] versus 13.55 months [95% CI (10.29 – 16.80)]; p-value of 0.208. Nevertheless, although there is no statistically significant difference in PFS between the two groups, the observed PFS in our study is overall shorter than the PFS durations published in phase III RCTs. To detail, in a phase III RCT comparing palbociclib plus letrozole to letrozole monotherapy, the median PFS of palbociclib was 24.8 months [95% CI (22.1 to not reached)] versus 14.5 months [95% CI 12.9 to 17.1)] for letrozole group (63). Whereas, in another analysis of an RCT comparing the addition of palbociclib to fluvestrant versus fluvestrant plus a placebo, the median PFS in the palbociclib group was 9.5 months [95% CI (9.2-11.0)] versus 4.6 months [95% CI (3·5-5·6)] in the

fulvestrant plus placebo group (64). In our study, the PFS for palbociclib group with all possible indicated combinations was 17.85 months [95% CI (15.11 – 20.59)]. This may be due to the relatively lower follow up period in our study compared to the published phase III trials about palbociclib. As for ribociclib, in a phase III RCT that compared the addition of ribociclib to AI versus AI monotherapy in the first line treatment of HR+/HER-2 stage IV breast cancer women who are postmenopausal, the former comparator had a longer PFS duration of 19.3 months (to not reached during the observational study period) versus 14.7 months in the AI group (60). Another phase III RCT (MONALEESA-3 trial) studied the efficacy of ribociclib and fulvestrant in the treatment of HR+/HER-2 stage IV breast cancer postmenopausal women showed that it had a median PFS of 20.5 months (95% CI, 18.5 to 23.5 months) versus 12.8 months in the traditional therapy in absence of ribociclib (61). A third study evaluated the addition of ribociclib to endocrine therapy versus endocrine monotherapy in premenopausal women also found a longer PFS in ribociclib group versus endocrine monotherapy group 23.8 months (95% CI 19.2-not reached) in the ribociclib group compared with 13.0 months (62). However, in our study the PFS for the palbociclib group was of 13.55 months [95% CI (10.29 – 16.80)]. Similarly, this may be attributed to the shorter duration of patients follow up in our study.

The OS was also of our efficacy outcomes in this study. The OS of palbociclib in our study was 29.82 months with a 95% CI of (27.26 – 32.39). In comparison with the published literature, again, the OS period we obtained in our study is compared lower than what was published in the studies. For instance, according to a published analysis in 2018 from the PALOMA-3 trial comparing the overall survival in the palbociclib group plus fluvestrant to the placebo plus fluvestrant as a main outcome, the overall survival in the palbociclib group was 34.9 months with a 95% CI of (28.8

– 40.0) in the palbociclib group (139). This can be also attributed to the shorter median follow up period in our study as well as the smaller sample size of our study compared to the published studies. As for the OS related to the ribociclib treatment arm, our study showed that ribociclib was associated with an overall survival 31.72 months with a 95% CI of (24.57 – 38.87) for all the study participants receiving ribociclib plus an eligible combination. In a recent published analysis evaluating the OS as the main outcome in postmenopausal patients receiving ribociclib plus fluvestrant, it was shown the addition of ribociclib to fluvestrant was associated with an OS of 66.9% at 42 months with a 95% CI (58.7 to 73.9) (140). In addition, in a recent published abstract for an analysis regarding the OS from the MONALEESA-7 trial (in pre/peri-menopausal women receiving ribociclib), the ribociclib treatment was associated with an overall survival of median 58.7 months versus 48.0 months in the placebo group; HR, 0.76 [95% CI (0.61-0.96)] (141). In our analysis, the follow up period itself was shorter which may not be reflective for the real overall survival. Moreover, the whole population was considered for the survival analysis without a subgroup analysis depending on the menopausal status as per these two previous analyses.

Although the effectiveness results were not based on subgroup analyses, we run a Cox-regression analysis to investigate the impact of the different baseline factors on the results of PFS and OS of the treatment arms. As indicated earlier, the COX regression analysis included the following factors: nationality, menopausal status, recipient of a previous hormonal therapy, diagnosis of metastasis (de novo or recurrent), site of metastasis, and the combination medication(s) with the CDK4/6 inhibitors. None of these factors had a statistically significant impact neither on the PFS nor on the OS as per our results. Therefore, relying on the analysis of palbociclib and ribociclib with all their different indicated combination treatments was valid and

reliable to generate the OS and PFS conclusions. Similarly, there was no need for a subgroup analysis based on nationality, menopausal status, recipient of hormonal therapy, diagnosis of metastasis or site of metastasis was not required since none of these factors had a significant impact on the efficacy endpoints. To date, there are no published head-to-head trials evaluating the effect of these factors on the conclusion of the effectiveness of the CDK4/6 inhibitors, e.g.: there are no published trials evaluating the effectiveness of palbociclib plus letrozole versus palbociclib plus fluvestrant on the PFS or OS. Therefore, this Cox-regression analysis confirmed that different indicated combinations medications with CDK4/6 inhibitors have no statistically significant effect on the overall effectiveness of CDK4/6 inhibitors in terms of PFS and OS; and therefore, can be used alternatively depending on the indication and suitability for different patients. The same conclusion could be drawn for the other factors included in this analysis as well.

Lastly, for the safety profile of the two treatments of interest, blood related side effects: neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, anemia, and pancytopenia were evaluated. Consistently with what was published in the treatments monographs, neutropenia was the most commonly reported side effect for both palbociclib (around 60% of the patients), and ribociclib (66.7%) which was also the mostly common blood-related side effects for both medications (57,97). However, febrile neutropenia occurred only in 3.7% of the patients in the palbociclib group. That was followed by the thrombocytopenia that occurred in 3.7% of the patients in the palbociclib and 7.4% of the patients in the ribociclib group, which is lower than what was published in the drug monographs (57,97). This may be due to the fact that our sample size was lower than what was conducted in the phase III trials and so was our follow up period.

Of note, this phase I of our study would have several impacts. First of all, it is considered the first retrospective observational study evaluating the efficacy and safety of palbociclib and ribociclib in the real world without the controlled environment of RCTs. It would help researchers and decision makers to confirm the findings of the published of RCTs in the real-world scenarios. In addition, it would help providing an insight not only about the efficacy, but also about the safety profiles of the medications. Worthy to highlight is that the number of patients on palbociclib were more than the number of patients on ribociclib. Therefore, this need to be addressed by future research.

5.2. Discussion of Phase 2: The Pharmacoeconomic Phase

In the second phase of this research, we aimed to make a thorough pharmacoeconomic evaluation for the CDK4/6 inhibitors in use in Qatar. We started by making a cost analysis study to summarize the cost of each of the two strategies in the different health states throughout the follow up period. This was followed by a modeling simulation to investigate the overall cost, the overall effectiveness, and the overall utility of the two treatment strategies and compare them in terms of the overall incremental cost-effectiveness and the overall incremental cost-utility. All in all, the cost-analysis revealed that the two treatment strategies have almost similar cost per patient per month with having ribociclib less costly than palbociclib, but the difference was not statistically significant. Although the drug acquisition cost of ribociclib is higher than palbociclib, the result of having the cost of ribociclib less costly than palbociclib were based on the real individual patient data obtained from the NCCCR. This may be explained by many factors such as: less frequent required lab tests monitoring, less required radiological or cardiac procedure monitoring, or less consumption in other related healthcare resources in general. A GLM was also

conducted to explore the effect of the baseline characteristics on the cost of the treatments. It was shown that none of the baseline characteristics were associated with a statistically significant effect on the costs except for age and the recipient of a prior hormonal therapy.

The main objective of this phase was to investigate the long-term cost-effectiveness and cost utility of the two CDK4/6 inhibitors in use in the State of Qatar. Therefore, a 10- year Markov's model was run to summarize the long-term cost (QARs), effectiveness (LYs), and utility (QALYs) for each of the two treatment strategies. Overall, ribociclib was found to be a more cost-effective option than palbociclib in terms of both cost-effectiveness and cost-utility. Moreover, in our base-case analysis, the treatment with ribociclib was overall dominant over palbociclib in terms of both ICER and ICUR. The finding of having ribociclib more cost effective than palbociclib remained robust against all the one-way sensitivity analysis included factors at the 3 GDP WTP threshold (cost-effectiveness threshold). For the 1 GDP WTP threshold (very cost-effectiveness threshold), only the uncertainity regarding one factor, the utility of PFS status in the ribociclib treatment arm, yielded an ICUR above the 1 GDP (198,120.3 QAR/QALY) suggesting that ribociclib is not a very cost-effective option. However, compared to the recommended 3 GDP WTP threshold as per the WHO, ribociclib is still a cost-effective option compared to palbociclib even with the uncertainty associated with that factor. Of note, our conclusion remained robust against the probabilistic sensitivity analysis that is associated with the combined uncertainties of all factors. Approximately 60% of the yielded hypothetical 10,000 scenarios in the Monte Carlo simulation suggested that ribociclib is more cost-effective than palbociclib.

To date, and up to our knowledge, there are four comparative

pharmacoeconomic evaluations regarding the cost-effectiveness and the cost-utility of palbociclib and ribociclib. The findings of our study were consistent with three of them. That is, in a study conducted in Spain by Galve-Clavo et. el (2018) to evaluate the ICER and ICUR of ribociclib plus letrozole versus palbociclib plus letrozole, the former was associated with an ICER of Euros 1,007.69 (QAR 4360.56) per every additional life year gained and an ICUR of Euros 1,543.62 (QAR 6,679.69) per each QALY gained, at a threshold of 30,000 Euros/ QALY (129,818.59 QAR) (116). Therefore, this study revealed that ribociclib was also more cost-effective and cost-useful compared to palbociclib from the Spanish National Health System perspective (116). In another study by Mistry R. et al. (2018) that conducted in the USA also comparing of ribociclib plus letrozole versus palbociclib plus letrozole versus letrozole monotherapy, ribociclib was dominant over palbociclib with a cost-saving of 43,037 USD, and also was still cost-effective compared to letrozole monotherapy option (98). That pharmacoeconomic analysis was conducted from the USA private third-party payer perspective at a WTP threshold of 198,000 USD/QALY (720,918.06 QAR/QALY) (98). Our findings were also consistent with one more pharmacoeconomic analysis by Suri G. et el (2019) conducted in the UK where also ribociclib plus letrozole was compared to palbociclib plus letrozole (118). Their study reported that ribociclib plus letrozole was a more cost-effective treatment strategy from the National Health Services (NHS) and Personal Social Services (PSS) perspective in the UK at a WTP threshold of 30,000 euro/QALY (118). Only in one cost-effectiveness study conducted in the USA, neither palbociclib nor ribociclib were cost-effective options, and the reason for this is that the ICER was calculated for each of the two comparators versus letrozole monotherapy (117). There was no incremental cost-effectiveness ration between the two CDK4/6 inhibitors, and therefore, none of them was cost-effective compared to letrozole monotherapy (117).

Although the previous pharmacoeconomic analyses were all of a high quality as per our evaluation for them on the QHES tool, we could not rely on their findings to Qatar settings for some reasons, and there was a need to conduct an economic analysis in Qatar for these CDK4/6 inhibitors. First of all, the generalizability of pharmacoeconomic analyses across the countries is sometimes impaired since the due to the different sources of price weights among different countries (142), and due to different perspectives from which the pharmacoeconomic analyses take place (143). Secondly, all used the published phase III clinical trials as the source for their simulated cohort, probabilities, effectiveness and utility endpoints. In spite of success of the analysis in the end, the use of these phase III trials itself is associated with some limitations since they were not designed basically to catch both clinical and economic endpoints. That is, in many of the pharmacoeconomic analyses based on RCTs, they try to summarize the economic outcomes from the pre-collected primary clinical outcomes, so the sources of the economic data are not primary (142). Both the MONALEESA and the PALOMA trials from which the four pharmacoeconomic analyses took their data were not predesigned to catch economic data. Therefore, we sought a predesigned source of data to rely on for our economic analysis and conducted our phase I and phase II of the project accordingly. Thirdly, the four pharmacoeconomic analyses all compared the use of palbociclib versus ribociclib with only one of the indicated combinations, letrozole. This is because of the fact that they used the same published phase III trials cohorts and interventions for their data. We sought a more thorough pharmacoeconomic analysis taking into consideration all the FDA approved treatment combinations; especially that the COX regression conducted in phase I concluded no statistically significant difference in terms of the efficacy between the different treatment combinations. As a result, our analysis filled these gaps providing a

powerful pharmacoeconomic analysis that can be doubtlessly used for decision makers in Qatar and other countries with similar health economic considerations.

5.3. Research Strengths and Weaknesses

Our project has some unique strengths on both the clinical and the pharmacoeconomic sides. To elaborate more, firstly, the clinical phase (phase 1) is considered the first retrospective observational trial evaluating the efficacy and the safety (PFS and OS) for the two used CDK4/6 inhibitors in Qatar. Observational studies are important tools to validate the performed RCTs in a real life without the application of too much control on subjects, and consequently, need to be implemented in real practice frequently (144). Secondly, to date, there is no head-to-head RCTs nor observational studies comparing palbociclib and ribociclib together at the same time. Consequently, our observational study is considered the first head-to-head comparison between palbociclib and ribociclib. Thirdly, one more strength related to the nature of the study itself is that the study was a well-designed observational study, which is normally ranked the fourth in terms of the validity and the low risk of bias in the hierarchy of the scientific evidence pyramid (145). Lastly, in the clinical phase, we run an exploratory Cox-regression analysis to investigate the effect of the different baseline characteristics on the PFS and OS. This Cox-regression analysis revealed an important finding suggesting that there is no statistically significant difference in PFS and OS between the different indicated combinations of the palbociclib and ribociclib.

In the second phase, the pharmacoeconomic phase, has also some strengths. Firsly, it is the first pharmacoeoconomic evaluation evaluating the cost-effectiveness and the cost-utility of CDK4/6 inhibitors in Qatar, Gulf region, and in Middle East and North Africa (MENA) region in general. Therefore, the findings of our current pharmacoeconomic analysis can be used locally and regionally in countries that have

similar economic profiles and healthcare systems with mild modifications to fit their context. Secondly, it is the first pharmacoeconomic analysis regarding these two agents that was based on actual settings and real-world individual patient data rather than just a simulation from clinical trials, avoiding all the disadvantages for modeling from clinical trials. Thirdly, it is the first pharmacoeconomic evaluation that compares palbociclib and ribociclib with all their FDA indicated combinations; other analyses compared only the CDK4/6 inhibitors plus letrozole. In addition, it included pre/post-menopausal females in the cohort unlike the other analyses that included only post-menopausal females as their cohort. Lastly, we performed an internal critical appraisal for our pharmacoeconomic study using the QHES tool to assure the quality of the produced analysis, so we can assume that our results are assured for validity with minimal bias.

Nonetheless, similar to any other research, our research had some limitations that need to be acknowledged. First of all, the total number of our population in the clinical phase is 108 patients. Compared to the other large trials, 333 - 700 patients, our sample size is small and may not be adequate. However, we could include all the patients that we had from 2017 to end 2019 as long as they meet the inclusion/ exclusion criteria. Therefore, this may be addressable by future research, or a future extension of the current research to include more subjects. Secondly, although the follow up duration was enough for the PFS event to occur, for the OS event, we believe that the follow up duration was not enough, and the reported results are immature. Even in the published phase III trials, the OS results were not mature as they need a long follow up duration. Thus, we were forced to report our OS data as they were. On the other hand, for the pharmacoeconomic phase, the main limitation is that we based our results on the clinical phase, which itself has some limitations and potential uncertainties. However,

we could address this limitation by incorporating both deterministic and probabilistic sensitivity analyses that relied on the phase III published RCTs. Our pharmacoeconomic conclusions remained robust against the uncertainties in both the deterministic and the probabilistic sensitivity analyses.

5.4. Implications and Recommendations

The present research has some important implications. First of all, it could validate the findings of the published clinical trials regarding the safety and the efficacy of palbociclib and ribociclib in real-world. Secondly, the findings of our research directly affect the decision-making process regarding the use of palbociclib and ribociclib in Qatar. In addition, they can be used regionally in countries that have similar economic profile and cost sources to Qatar such as the GCCs. Moreover, the pharmacoeoconomic phase is considered the fifth pharmacoeoconomic evaluation concerning these two medications worldwide. Therefore, the combination of these pharmacoeconomic evaluations from different countries with different economic considerations and different perspectives can give a thorough insight about the long-term cost-effectiveness of these two medications.

Based on our study findings, we have several recommendations for the current practice and for the future research. Firstly, our study findings suggest keeping both palbociclib and ribociclib as formulary medications in the NCCCR, and to use ribociclib more being more cost-effective when tolerable and applicable. Secondly, during the data collection duration for the clinical phase, we noticed an exclusion of 37/145 potentially eligible medical records due to not meeting the inclusion/exclusion criteria. Our inclusion/exclusion criteria were mainly based on the local and the international guidelines. Therefore, all the excluded records are assumed not to be matching to the international records. As a result, we would recommend conducting a

local audit study to explore this practice and to put solution to reduce it. This issue can be present in international settings as well, so we recommend frequent auditing for wrong practices to put guidelines to resolve them. Thirdly, since ribociclib had a lower overall cost than palbociclib although it has a higher acquisition cost in general, further evaluation about the consumption of the related resources needs to be conducted in the future, but with a larger sample size for both treatment arms. Another important recommendation from our study is that there is a need for quality-of-life (QoL) studies for cancer patients in different health states. We could only rely on the international published data for the QoL to estimate the utility values due to the lack of local or regional QoL data. Lastly, all the published pharmacoeconomic agents included only palbociclib and ribociclib in their analyses. Ambeciclib is another CDK4/6 inhibitor that was never addressed by pharmacoeconomic evaluations. Thus, more comparative pharmacoeconomic evaluations need to be conducted about this medication along with the other two medications in the same CDK4/6 inhibiting family.

5.5. Conclusions and Future Directions

Since their introduction to the market, the use of CDK4/6 inhibitors is increasing due to their proved clinical efficacy. In this research, we confirmed the clinical benefit of two of the CDK4/6 inhibiting agents, palbociclib and ribociclib. In addition, we compared them head-to-head for the first time. Our findings showed that there was no significant difference in terms of their PFS or OS. In addition, the distribution of the ADRs between the two treatments was balanced, suggesting that the two treatments have equivalent safety profiles. Other factors that may be thought to affect the efficacy of the two medications were also evaluated. We proved that these factors, such as the type of the combination medication, have no significant effect on the effectiveness of the two CDK4/6 inhibiting medications.

From a pharmacoeconomic point of view, the short term direct medical costs of the two treatment strategies considering all the contributing components of their costs were analyzed suggesting that both treatment strategies have similar short term direct medical costs. This finding was further projected for 10 years using a well-designed Markov's model which showed that there ribocicliclib is more cost-effective than palbociclib at a 3 GDP threshold and at a 1 GDP threshold suggesting that ribociclib should be a more favorable option over palbociclib in the practice whenever applicable. Lastly, this conclusion remained robust against the different single uncertainties. In addition, it remained robust in approximately 60% of the results of the combined uncertainties using the probabilistic sensitivity analysis. As a result, ribociclib was proven to be generally more cost-effective than palbociclib in the state of Qatar. This finding can be generalizable to countries having similar economic profile, consideration, and cost derivers to Qatar.

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APPENDICES

Appendix 1. Ethical Approval Letter from MRC

2/2/2020

مؤسسة حمد الطبية
Hamad Medical Corporation
Hamad
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث

APPROVAL LETTER
MEDICAL RESEARCH CENTER
HMC, DOHA-QATAR

Ms. Shereen Amin Mahmoud Elazzazy **023013** **Assistant Director Clinical Pharmacy** **Pharmacy** **National Center for Cancer Research (NCCCR)** **Hamad Medical Corporation**	**Date: 30th January 2020**
Protocol No.	MRC-01-19-318
Study Title	Cost?Effectiveness Analysis of the Use of Ribociclib Versus Palbociclib for Hormone? Receptor?Positive and HER2? Negative Stage?IV Breast Cancer in Qatar
The above titled research study has been approved to be conducted in HMC summarized as below:	
Study type:	Data Review
Data Collection Period:	01/01/2016 ? 01/06/2019
Team Member List:	Dr. Anas Ahmad E A Hamad , Dr. Salha Mohd. Bu Jassoum , Ms. Nour Hisham Alziftawi , Ms. Shereen Amin Mahmoud Elazzazy , Prof. Mohamed Izham Mohamed Ibrahim
Review Type :	'Exempt' under MOPH guidelines "Category 3: Research involving the collection or study of existing: Data, documents, records and the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects".
Decision :	Approved
Hospitals/ Facilities Approved:	National Center for Cancer Research (NCCCR)

This study must be conducted in full compliance with all the relevant sections of the Rules and Regulations for Research at HMC and the Medical Research Center should be notified immediately of any proposed changes to the study protocol that may affect the `exempt` status of this study. Wherever amendments to the initial protocol are deemed necessary, it is the responsibility of the Principal Investigator to ensure that appropriate reviews and renewed approvals are in place before the study will be allowed to proceed.

1/2

Please note that only official, stamped versions of the approved documentation are to be utilized at any stage in the conduct of this study. The research team must ensure that progress on the study is appropriately recorded in ABHATH, the online research system of the Medical Research Center.

We wish you success in this research and await the outcomes in due course.

Yours sincerely,

Prof. Michael Paul Frenneaux
Chief of Scientific, Academic and Faculty Affairs
Hamad Medical Corporationn

Date: 30 January 2020

Appendix 2. Approval Letter from QU-IRB

Qatar University Institutional Review Board **QU-IRB**
QU-IRB Registration: IRB-QU-2020-006, QU-IRB, Assurance: IRB-A-QU-2019-0009

February 10th, 2020

Dr. Mohamed Izham Mohamed Ibrahim
College of Pharmacy
Qatar University
Phone: +974 4403 5580
Email: mohamedizham@qu.edu.qa

Dear Dr. Mohamed Izham,

Sub.: Research Ethics Review Exemption
Project Title: "A cost-Effectiveness Analysis of the Use of Ribociclib Versus Palbociclib for Hormone-Receptor-Positive and HER2- Negative Stage-IV Breast Cancer in Qatar"

We would like to inform you that your application along with the supporting documents provided for the above project, has been reviewed by the QU-IRB, and having met all the requirements, has been granted research ethics **Exemption** based on the following category(ies) listed in the Policies, Regulations and Guidelines provided by MoPH for Research Involving Human Subjects:

Exemption Category 3: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified.

Documents reviewed: QU-IRB Application Human Subject- V3, QU-IRB Application Material Check List copy, Protocol Edited, HMC Approval (Approval), data collection sheet, QU-IRB Review Forms, responses to IRB queries and updated documents.

Please note that exempted projects do not require renewal; however, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

Your Research Ethics Approval Number is: **QU-IRB 1231-E/20**. Kindly refer to this number in all your future correspondence pertaining to this project. In addition, please submit a closure report to QU-IRB upon completion of the project.

Best wishes,
Dr. Ahmed Awaisu
Chairperson, QU-IRB

Institutional Review Board
(IRB)
Office Of Academic Research

Appendix 3. Full Implemented Markov's Model Inputs and Paths from TreeAge Pro ®

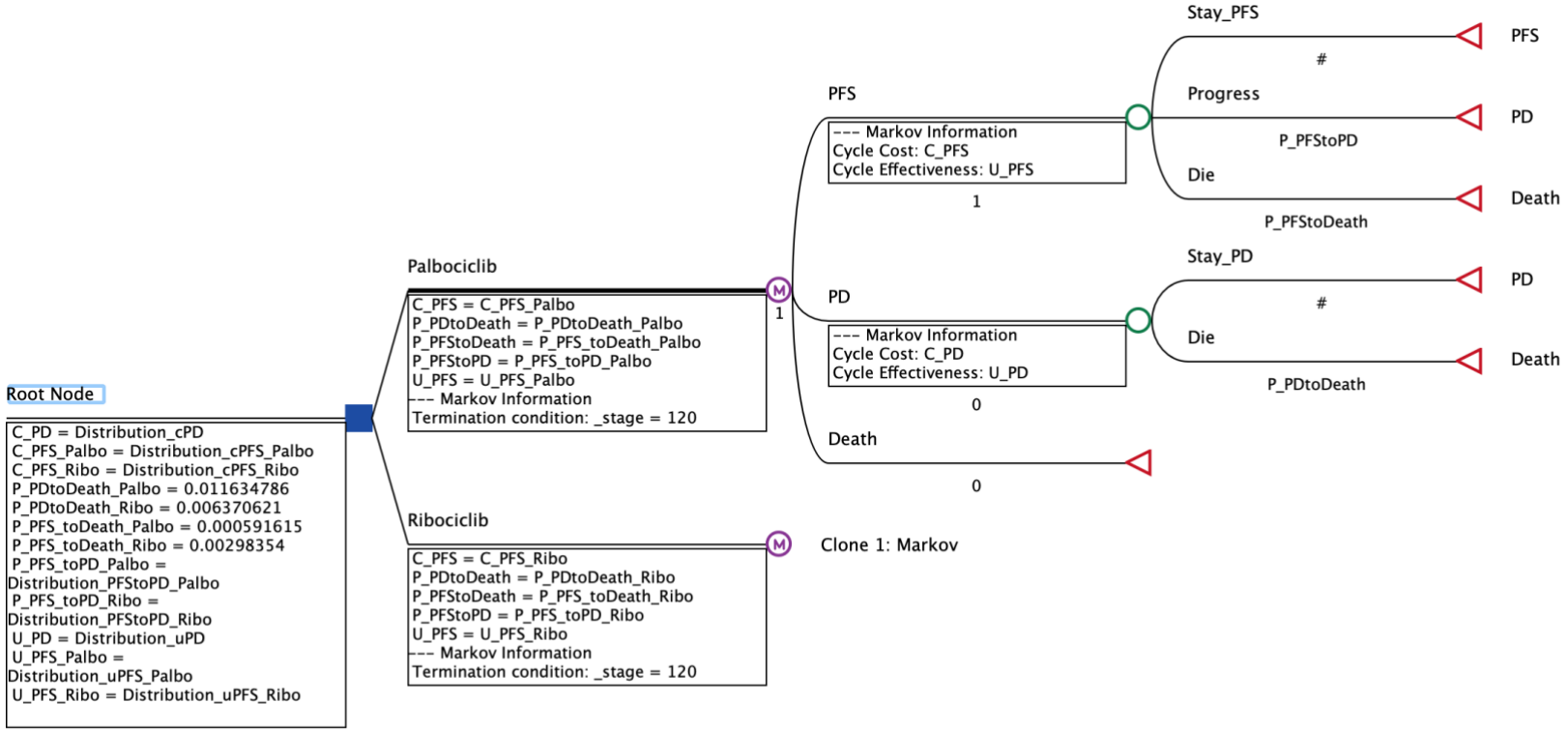

Figure 12. The detailed Markov's Model inputs and pathways from TreeAge Pro ®. M is a Markovian node. Open circle is a chance node. Triangle is a terminal node. 'Clone 1: Markov' means that the pathways are a copy from M-1 node.

Appendix 4. Demonstration Example for the Transition Probabilities Calculation

Aim: To calculate the transition probability for palbociclib cohort form the PFS to PD status.

Given: median follow up for PFS was 17.33 months (1.44 years). Number of patients who developed progression over this time equals 45. Number of the total cohort on palbociclib equals 81.

Calculation steps:

1- Cumulative probability for developing progression from PFS = 45/81= 0.556

2- The rate of the progression even = $-\frac{\ln(1-0.556)}{1.44} = 0.56$

3- The 1-month probability of the progression event= $1 - \exp\left(-0.56 \times \frac{1}{12}\right) = 0.045$